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THE INTRACAVITARY ADMINISTRATION OF RADIOACTIVE COLLOIDAL GOLD*

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BOSTON

IN THE comparatively short time since its introduction by Sheppard and Hahn[1] in 1947, radioactive colloidal gold (Au 198) has come to be used frequently in the palliation and treatment of neoplastic disease.[2] The increasing importance of this radioactive isotope is due to the clinical usefulness imparted to the material by its particular physical and chemical properties.[3, 4] The isotope is prepared by the irradiation of gold foil in the nuclear reactor pile at Oak Ridge, Tennessee. The foil is converted by aqua regia to gold chloride, which is reduced to metallic gold by ascorbic acid in the presence of excess gelatin. The gold is now present as a suspension of colloidal particles varying in size from 0.001 to 0.003 microns. Radiogold has a half-life of two and seven-tenths days, which is sufficiently long to be practical and yet short enough to avoid long-continued irradiation of the patient and thus to lessen the remote possibility of late carcinogenesis. Since the material is in the metallic form, it is insoluble and chemically inert. Thus, it has none of the toxicity of gold salts. This insolubility also contributes to the most useful of its properties: its capacity to remain indefinitely where it is introduced into the body when injected into tumor tissue or into a serous cavity. There is a small but desirable spread via the lymphatics, owing to macrophages that phagocytose the colloidal particles and then migrate along the lymphatics. An insignificant amount enters the blood stream after interstitial or intracavitary injection. The colloidal gold represents a suspension of a multitude of particles (10 trillion particles in 50 mc.), each of which is a point source of radiation. This radioactivity consists of an effectively strong β particle radiation (0.98 Mev), which has a maximum range of about 3.8 mm. and a "half-path" of approximately 0.4 mm. in tissue, coupled with a penetrating γ ray of 0.41 Mev, which permits one to trace, by external Geiger–Müller counters, the distribution of the isotope within the body. It is the β radiation that accounts almost entirely for the radiation effects produced on the tissues. In addition, the concentration of radiogold in excreta is negligible,[5] greatly simplifying the problem of protection of those caring for the patient.

The usefulness of this isotope is enhanced by the fact that it can be administered by several routes, each producing a different end result. When given intravenously the colloidal gold particles are taken up by the reticuloendothelial system (80 to 95 per cent in the liver and spleen, with lesser concentrations in the lymph nodes and bone marrow).[1, 6-8] Thus it can be used in the treatment of the lymphomas and chronic leukemias with results similar to those obtained with the usual methods of therapy.[3, 9] When the particles are injected directly into inoperable tumors, the lesions may regress or even disappear.[2, 9-13] It is difficult, however, to obtain a uniform spread of the radiogold throughout the tumor tissue and sometimes impossible to follow the course of trabeculated, irregular tumors.[14] In the injection of soft or necrotic tumors there is also the hazard of leakage of the colloid out of the tumor. Awkward and heavy lead-shielded syringes must be used to reduce exposure of the operator to safe levels of radioactivity. The material has been inserted directly into the bronchi in cases of bronchogenic carcinoma[15, 16] and has also been injected, as larger particles, into the pulmonary artery and its branches, lodging in the capillary bed of the lung.[17] In this hospital it is being instilled into the empty hemithorax after pneumonectomy for carcinoma of the lung, with the object of possibly destroying any remaining cancer tissue in the cavity not accessible to surgery. There is less likelihood that a cancerocidal dose of radiogold will be concentrated in the lymphatics draining this region. Curative results may be possible in cases in which the neoplasm has seeded over the pleura without evidence of more distant spread. Other workers have recently been following this procedure.[18]

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Intrapleural and Intraperitonal Administration

Radioactive gold has found its greatest success and widest application, however, in the attempt to eliminate the intractable formation of fluid in the pleural and peritoneal cavities in carcinomatosis. Dosage of radiogold in common use ranges from 25-100 millicuries instilled into the pleural space to 50-200 millicuries into the peritoneal cavity, as a single dose. Numerous reports[2, 19-26] attest to its efficacy in slowing or stopping fluid formation in patients previously requiring tapping at intervals as frequent as a week or less. In favorable cases, further drainage of fluid may not be necessary, whereas in others, after one or more additional withdrawals, fluid may cease to accumulate. When the effusion is bloody, the first effect noted may be a clearing of the fluid.

Favorable results have been obtained in 30 to 90 per cent of cases in the few series reported to date. The degree of success attained appears to be related directly to the maintenance of strict criteria in the selection of cases. Ideally, the patient selected for radiogold therapy should be one in whom no large masses of tumor are present in the cavity and who has no severe constitutional effects from the neoplasm, apart from the discomfort and disability occasioned by the massive fluid accumulation. If bulky tumor masses are present, radiogold therapy is likely to be ineffectual; x-ray therapy should be more advantageous. In the ideal cases, radioactive gold has proved to be more effective than irradiation in controlling fluid formation, as well as being more convenient and less upsetting to the patient, since radiation sickness rarely occurs, and then only in a very mild form.

This cessation of fluid formation may be due partly to a lethal effect on free cancer cells in the fluid[19]; to the irradiation of the numerous small tumor seedings on the serosal surfaces; and to the radiation effects on the mesothelium and small blood vessels of the serosa. Fibrosis over the surface of the tumor and of the serous lining, occasionally to a marked degree, has been found after some months in several, but not all, patients treated with radiogold and later succumbing to their neoplastic disease.[27, 28] The radiation produces an obliteration of the minute blood vessels supplying the serous lining of the cavity. Thus it may be conjectured that fluid formation is slowed by the suppression in the cavity (free tumor cells and tumor seedings) and by the reduction of fluid passage into the cavity owing to submesothelial fibrosis and a reduced blood supply.

Hazards of Administration

In patients with pleural involvement and in the majority of those with peritoneal involvement, the fluid is relatively thin in consistence and is not significantly loculated. Such an effusion can readily be withdrawn through a needle or trocar, and the radiogold instilled by the same route. Some cases of peritoneal involvement, however, present complicating factors. When there is loculation of the fluid from extensive adhesions or when the contents are extremely viscid (for example, in pseudomyxoma peritonei), administration of the gold by this trocar method may have undesirable results. At best it may end in an ineffectual distribution of the radioactivity. In less favorable circumstances, a pocketing of the material in a small space may occur, with the danger of necrosis of bowel, other contents of the cavity or the abdominal wall itself. (The development of intraperitoneal abscesses, causing cutaneous fecal fistulas and a rectovaginal fistula, in 2 patients in whom large quantities of radiogold were instilled into fibrotic, relatively avascular areas has recently been reported.[29]) In addition, perforation of the bowel may result from blind trocar introduction when the intestine is immobilized by tumor growth, adhesions from old incisions, previous tappings or other local pathologic states. For these reasons, caution must be observed in the use of this potentially dangerous therapeutic agent.

In view of the increasingly widespread use of radioactive colloidal gold for instillation into serous cavities and of the hazards described above, it is believed that a discussion of the methods used at this institution may be of interest, including a description of a convenient remote technic of delivering the radiogold to the patient.

Preparation of Patients for the Introduction of Radioactive Colloidal Gold

The usual case presents no particular problem. Paracentesis is performed, the fluid is withdrawn, and the gold suspension is then instilled, by the technic described below in the next section, into the cavity through the trocar, after it has been determined that a free flow is still present. A small catheter or plastic tubing may be threaded through the trocar, the trocar withdrawn, and the gold suspension injected into the patient via the catheter or tubing. This doubly ensures that the material enters the cavity and is not inadvertently injected into tissue. Patients falling into the complicated group described above, however, have been prepared by operative means for delivery of the gold.

With suitable minimal amounts of general anesthesia, since relaxation is not required, an appropriate incision is made. Pre-existing radiodermatitis, tumor masses themselves or other factors may influence the choice of incision. A transverse epigastric incision with lateral retraction of rectus-muscle bellies has been employed in our cases. After evacuation of fluid and other material from the cavity, followed by biopsy and exploration with an attempt to free any major loculations, a No. 16 or No. 18 hard-rubber urethral catheter is introduced into

each lumbar gutter at the level of the third or fourth lumbar dermatome. Such catheter placement allows subsequent delivery of the radiogold into each of the two major free peritoneal compartments, the right and left sides of the mesenteric attachment. Holes are cut along the sides of the catheter ends to favor free and wide distribution of the instilled material. The catheters are led through stab wounds just below the lateral angles of the incision, and then obliquely through subcutaneous tunnels in fat, entering the peritoneum through offset stab wounds. This allows complete primary closure of the exploration wound with nonabsorbable cotton sutures and minimizes any possible danger of contamination of the larger wound with radioactive material. The skin is sutured snugly about the catheters, and sutures placed if necessary to draw the skin edges together after the catheters have been removed. An additional suture is placed and tied about each catheter to prevent accidental withdrawal before use; this is cut when the catheter is removed. Catheter ends are tied or clamped off (after testing for patency and free flow with saline solution) and incorporated in a sterile dressing placed separately from the primary wound dressing. The patient is then transported to his room, where, as described below, the radioactive material is instilled under more convenient circumstances for all personnel. Because of possible accidental contamination of the room where the radioactive material is administered, it seems best to handle it in the patient's room rather than in the operating suite, where a greater inconvenience might result from such an accident.

Technic of Radiogold Instillation

Delivery of the gold suspension to the patient is effected in a manner to minimize radiation exposure to personnel and to avoid possible contamination of the field. The radiogold is supplied by the distributor* in sealed, sterile, rubber-capped bacterin bottles. On receipt of the shipment this bottle is removed with long-handled forceps from the shipping container and placed behind a lead shield, and the activity (as quoted by the supplier) is checked by an ionization chamber of the "cutie-pie" type at 1-meter distance. (One millicurie reads 0.24 milliroentgens per hour at 1 meter, with an error of measurement within ±10 per cent.) If there is more activity than is desired, the excess gold is withdrawn. The quantity ordered, however, is precalculated to have the exact activity required for the case at the time of injection, so that no such withdrawal is necessary as a rule. The bottle is then placed in a lead container with a wall 19 mm. in thickness. A lead cover with a 4.8-mm. central hole is placed over the container. A curved, 17-gauge needle (inflow tract) is inserted into the bottle with the point remaining above the surface of the gold. A second such needle (outflow tract) is inserted to the bottom of the fluid. A lead cover with a narrow slot to accommodate the needles is placed over the first cover to minimize radiation from the container. With the use of 100 mc. the activity is less than 5 milliroentgens per hour at the outside surface of the container and 14 milliroentgens per hour directly over the slot. To the first needle is attached a three-way stopcock, leading to a 50-cc. syringe and a flask of sterile physiologic saline solution. The second needle is attached to 3.2-mm. disposable plastic tubing. This tubing can connect by appropriate adapters either to a paracentesis needle or to a catheter. By forcing saline solution from the syringe into the sealed bacterin bottle, the gold suspension is displaced from the bottle into the tubing and is rapidly delivered to the patient. It can be washed through with any desired quantity of saline solution. This serves the double purpose of diluting the colloid and "flushing out" the delivery system to rid the apparatus of all but a minute amount of radioactivity. The quantity of saline solution used here has varied from 70 to 200 cc. in chest cases and from 200 to 500 cc. in abdominal cases. All connections are of the interlocking type, and the tubing is tied on to connectors for added safety. The system, therefore, is capable of withstanding great pressure without leakage, although such pressure should never be necessary. Sterile precautions are observed throughout the procedure.

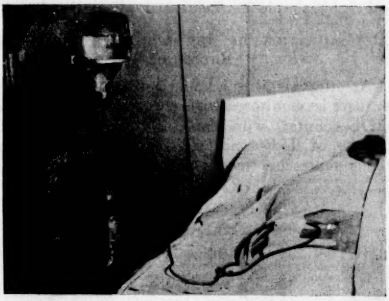

Figure 1. *Equipment Assembled for Injection of Radiogold Intraperitoneally via a Catheter in Each Lumbar Gutter in a Patient with Peritoneal Seeding and Ascites from Ovarian Carcinoma.*

The exposure to radioactivity of the physician and other attendants is small, since all are able to remain at a distance from the radioactive material. The radiation exposure to the physician injecting the radiogold averages 2 milliroentgens during the

*The radioactive colloidal gold used here is obtained on allocation from Abbott Laboratories, North Chicago, Illinois, through authorization of the United States Atomic Energy Commission.

administration of 100 mc. If a physician is steadying the trocar he receives about 5 milliroentgens. These values are small when one considers that 50 to 100 milliroentgens is received during the taking of an x-ray film of the chest.

When two catheters are used, these may be connected to a three-way stopcock attached to the outflow tract (Fig. 1). With knowledge of the volume of the gold suspension in the bacterin bottle and the capacity of the outflow tract leading to the stopcock, it is possible to direct approximately half the suspension down one catheter and half down the other by simple mathematical calculation.*

Determination of the Distribution of the Radiogold

At intervals after administration of the gold the patient is monitored, using a portable rate meter (IDL counter) with the G-M tube shielded by a T-tube of 15.9-mm. lead for sharp collimation. (This represents merely an expedient application

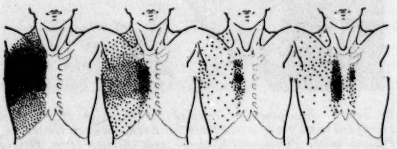

Figure 2. *Diagrams of the Distribution of Radiogold at Successive Intervals in the Empty Hemithorax after Pneumonectomy (from Left to Right, Twenty-Four Hours, Four Days, Seven Days and Twelve Days).*

Note the increasing localization in the mediastinum.

of apparatus already on hand). Thus at intervals the extent of spread of the colloid throughout the cavity can readily be determined by measurements taken at the skin surface (Fig. 2). It has been shown that the activity is initially moderately well distributed when this catheter technic is used (Fig. 3). In no case has there been soiling of the wounds with the radioactive gold at the time of injection or from subsequent seepage of the colloid. The distribution can be made almost uniform with a minimum of posturing, in contrast to the trocar method, in which considerable tilting and turning of the patient may be necessary to effect a uniform distribution. The patient merely changes position at hourly intervals throughout the first waking day and subsequently only as required if distribution is not uniform. This is of great advantage in those who are weak, uncomfortable or debilitated.

Health Physics

Protection of Personnel

As already indicated, the exposure of personnel to radiation is small at the time of instillation of the colloidal gold. After the injection the patient

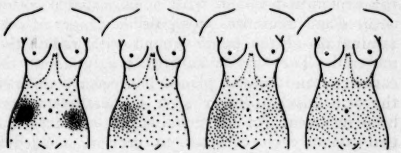

Figure 3. *Diagrammatic Representation of the Development of a Uniform Distribution of Radiogold after Intraperitoneal Administration (from Left to Right, One-Half Hour, Three and a Half Hours, Nineteen Hours and Seven Days).*

becomes a source of radiation, and measures to protect others must be taken. When 100 mc. is given there is usually emitted an activity measuring 50 milliroentgens per hour at the edge of the patient's bed and 5 milliroentgens per hour 5 feet from the patient. The patient must be at least 6 feet from other patients. A nurse is permitted to be within 2 feet of such a patient for a maximum of twenty minutes or at a distance 2 to 5 feet for ninety minutes a day. This is calculated to fall within the value specified by the National Bureau of Standards for maximum permissible exposure to radiation of 50 milliroentgens per day[30] and to allow for an additional 20 per cent safety factor. These periods can be doubled after three days, owing to the decay of the radioisotope. In addition, the nurses are rotated so that a different nurse cares for the radioactive patient each day. All personnel involved are required to wear film badges, which are changed once a week.

The equipment used for the injection is rinsed in a continuous-flow bath for several hours. Then it is set aside for a period of at least two half-lives before it is monitored and sterilized for re-use. It is considered safe to employ the apparatus when its radioactivity has fallen to 0.1 milliroentgens per hour.

Complications

The usual absence of the syndrome of radiation sickness, which invariably follows irradiation of similar magnitude given by x-rays, is a noteworthy feature of radiogold therapy. (One hundred mc. of radiogold inserted into the peritoneal cavity delivers

*For example, if one assumes that 100 mc. of radiogold is contained in a volume of 10 cc. — that is, 10 mc. per cubic centimeter — in the bacterin bottle and that the capacity of the outflow tract is 6.5 cc. (as it is in our apparatus), the injection of 6.5 cc. of saline solution from the syringe into the bottle will fill the outflow tract up to the stopcock. The activity of the suspension present in the tubing should be the average of the activity of the original solution (10 mc. per cubic centimeter) and the activity of the solution after dilution $\left\{\frac{100 \text{ mc.}}{10+6.5 \text{ cc.}}\right\} = 6 \text{ mc./cc.}$ — that is, $\frac{10+6 \text{ or } 8 \text{ mc./cc.}}{2}$

The total activity in the tubing is therefore (8 mc./cc. x 6.5 cc.) =52 mc. A second injection of 6.5 cc. will send this amount down the first catheter, and the activity remaining is directed down the second catheter after the stopcock has been adjusted. Both catheters are now flushed out with saline solution. Since this calculation is worked out in advance 13 cc. is injected in one maneuver. This method is admittedly subject to a considerable error but a strictly even division of the dose into two equal parts is not necessary.

3000 r equivalents physical to the serosa.[21]) Nevertheless, in a considerable number of cases in which catheters have been inplanted in the abdomen and radiogold instilled, some degree of adynamic ileus with nausea and vomiting has supervened. This may prove very troublesome and disturbing if not vigorously combated. It is not considered to be due to the radioactive gold per se, since it is not usually found in cases in which the gold suspension is instilled through a trocar into the abdomen and since no ill effects have been encountered in any of the chest cases. The ileus appears to be due to a combination of anesthesia, surgery and manipulation of the bowel, with supervention upon these factors of the radiation effects of gold on the radiosensitive intestinal mucosa. It is now our policy to institute, as soon as the surgery and gold instillation are completed, prophylactic measures against the possible appearance of this complication. This has proved satisfactory in lessening the incidence and severity of this adverse sequela. In the range of dosage employed, there has been no apparent depressant effect on the hematopoietic system. Others have occasionally noted a slight drop in white-cell count after intracavitary doses of 200 mc.[27] Consistent effects are not encountered until doses of greater than 200 mc. are used.

At this institution clinical results of the use of radioactive colloidal gold to halt fluid formation in the pleural and peritoneal cavities, as well as its efficacy as an adjunct to surgery in bronchogenic carcinoma, will be presented in subsequent reports.

Summary

The properties and clinical applications of radioactive colloidal gold (Au 198) are briefly reviewed, with special reference to the management of selected cases with recurrent pleural effusion or ascites due to malignant neoplasms.

A technic considered to be safe and effective in the administration of radiogold to patients with viscid or loculated ascites is described.

A closed remote system suitable for instilling the material into the pleural or peritoneal cavity is presented. This method was devised to simplify handling, to minimize exposure of personnel to radiation and to reduce the possibility of spillage and radioactive contamination.

We are indebted to Dr. Shields Warren, director of the Cancer Research Institute of the New England Deaconess Hospital, for his aid and advice in the preparation of this paper, and to the Biophysics Department of the Institute for providing the data on health-physics protection.

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ERYTHROBLASTOSIS FETALIS*

VIII. Studies of Serum Bilirubin in Relation to Kernicterus

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BOSTON

ALMOST important complication of erythroblastosis fetalis is brain damage, commonly known as kernicterus,[1] which has in the past affected about 15 per cent of liveborn infants with erythroblastosis. About 70 per cent of babies with kernicterus die within seven days of birth, and many of the remainder succumb during the first year to infectious diseases. Kernicterus is thus the most important cause of post-natal death in erythroblastosis fetalis. Babies with kernicterus who do not die have permanent neurologic sequelae, and constitute perhaps 10 per cent of all cases of cerebral palsy. Kernicterus has been proved to be preventable by exchange transfusions,[2] and the prevention of kernicterus has become the most important consideration in the treatment of erythroblastosis fetalis, dictating the necessity for prenatal investigation of Rh-negative women so that advance preparation may be made for the treatment of the baby.

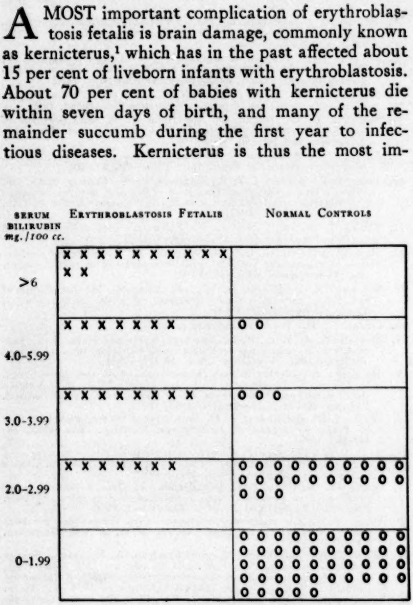

FIGURE 1. *Serum Bilirubin Levels of Blood Samples from Umbilical Cord in Normal Infants and Infants with Erythroblastosis.*

The brain damage is not present at birth.[1] It becomes manifest most commonly late in the second day of life, when opisthotonos is the most frequent and characteristic symptom. It does not occur in the absence of considerable jaundice. There has recently been much interest in the relation of jaundice to kernicterus, but, although erythroblastosis is commonly referred to in the literature as "icterus gravis neonatorum," there is, paradoxically, an almost complete absence of useful quantitative data concerning the icterus itself. Vaughan, Allen and Diamond[1-3] have shown that there is a close relation between the apparent severity of jaundice and the frequency of clinical kernicterus. Mollison and Cutbush[4, 5] have pointed out that the peak bilirubin concentration is apparently related to the liability to develop signs of kernicterus. The present paper deals with determinations of serum bilirubin in 229 infants with erythroblastosis fetalis and demonstrates a relation between high serum bilirubin levels and the occurrence of kernicterus.

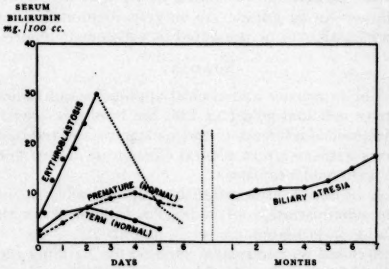

FIGURE 2. *Average Total Serum Bilirubin Levels of Infants with Erythroblastosis Compared with Those of Normal Infants, Premature Infants and Infants with Atresia of the Bile Ducts. In erythroblastosis, the black line represents the levels prior to treatment, and the dotted line the levels after treatment with exchange transfusion.*

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Methods and Materials

The serum bilirubin tests were performed by the method of Malloy and Evelyn[6] as modified by Ducci and Watson.[7] Recently, a micro modification of the method[8] has made it possible to obtain satisfactory results from capillary blood at frequent intervals, thus making it practical, for the first time, to follow changes in bilirubin levels several times a day, in newborn infants, from whom venous blood cannot be drawn.

All the infants studied were seen at the Boston Lying-in Hospital, the Children's Medical Center and the Beth Israel Hospital, Boston, during the years 1949–1952. All were infants with erythroblastosis that was due to anti-A, anti-B, anti-C, anti-E or anti-D. Since only a few were followed serially every few hours, most of the bilirubin levels recorded do not represent the maximum levels actually reached in the individual babies. Furthermore, since most of the infants were treated by exchange transfusions, the values obtained were even lower than the maximum levels that would have been reached had exchange transfusions been withheld. In spite of these limitations, the results obtained are of considerable value.

Results

The total serum bilirubin levels of blood samples from the umbilical cord are shown in Figure 1. Of 73 normal infants, 68 (93 per cent) had levels below 3 mg. per 100 cc., whereas of 34 infants with erythroblastosis, 27 (79 per cent) had levels above 3 mg. per 100 cc. It is evident that although cord bilirubin levels of infants with erythroblastosis are generally higher than those of normal infants, overlapping occurs between the two groups, thus limiting somewhat the value of cord serum bilirubin tests in diagnosis.

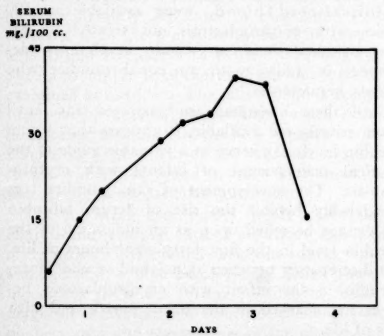

Figure 3. *Total Serum Bilirubin Levels of an Infant with Erythroblastosis Due to Anti-D Incompatibility Who Received No Treatment. (Signs of Kernicterus Developed at Eighty Hours of Age.)*

The average total serum bilirubin levels of infants with erythroblastosis prior to treatment are shown in Figure 2. It can be seen that the rise of serum bilirubin is much more rapid than in normal and premature infants. In babies with biliary atresia serum bilirubin does not reach the high levels seen in erythroblastosis fetalis.

The bilirubin levels of an infant with erythroblastosis who did not receive exchange transfusion are shown in Figure 3. Bilirubin rose steadily until the baby was two and a half days old and then started to fall. Clinical signs of kernicterus developed at eighty hours of age, fourteen hours after the bilirubin had apparently reached its peak and was already falling.

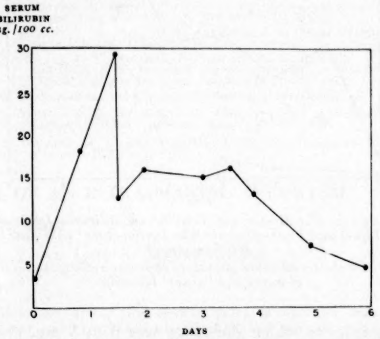

Figure 4. *Total Serum Bilirubin Levels of an Infant with Erythroblastosis Treated with Exchange Transfusion at One and a Half Days of Age.*

The bilirubin levels of an infant treated with exchange transfusion are shown in Figure 4. It can be seen that the serum bilirubin level is markedly lowered by exchange transfusion. This drop is due to a combination of removal of about 85 per cent of the baby's circulating red cells, which are the only important source of bilirubin, and removal of circulating bilirubin. There is usually an upward rise of bilirubin in the hours immediately after the transfusion. This is probably due primarily to the re-equilibration of the plasma and extravascular bilirubin.

As in other hemolytic diseases, the elevation is limited to the indirect fraction of the bilirubin, the "one-minute" or "direct" bilirubin remaining normal. The "one-minute" bilirubin becomes elevated in erythroblastosis only when the "inspissated-bile syndrome" occurs (Fig. 5). This condition is described in detail elsewhere.[9]

The relation of high serum bilirubin to the development of kernicterus is shown in Figure 6. Despite the fact that the data are biased in the

direction of low bilirubin because few maximum levels were obtained, the figures show that almost all the cases of kernicterus occurred in the infants with high bilirubin levels in each age group. In

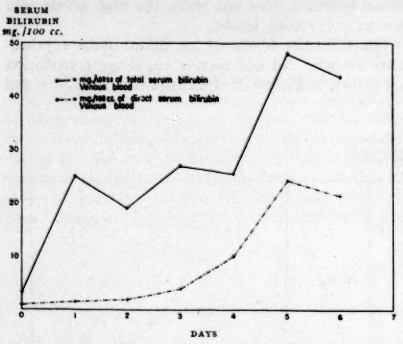

FIGURE 5. *One-Minute and Total Serum Bilirubin Levels of an Infant with Erythroblastosis Who Developed the "Inspissated-Bile Syndrome."*

The rise of total bilirubin after three days was entirely the result of increase in "direct" bilirubin.

the cases in which the range was 0 to 5 mg. per 100 cc., there was no kernicterus; in those in which the range was 6 to 15 mg. per 100 cc., there was a 3 per cent incidence of kernicterus, all in infants

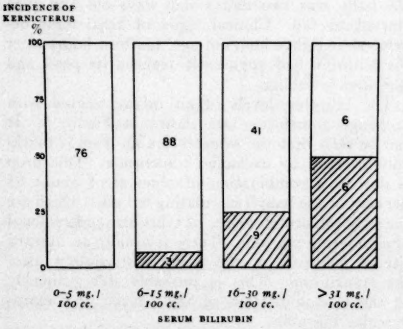

FIGURE 6. *Serum Bilirubin Levels and Incidence of Kernicterus in 229 Infants with Erythroblastosis. (Figures in Shaded Areas Represent the Babies with Kernicterus, and Figures in Clear Areas Those Without Kernicterus.)*

whose only bilirubin determination was obtained in the first two hours of life. The levels undoubtedly rose much higher in the next forty-eight hours. Kernicterus occurred in 18 per cent of the infants whose serum bilirubin was recorded at a level between 16 and 30 mg. per 100 cc. and in 50 per cent of those in whom levels above 30 mg. per 100 cc. were seen.

Discussion

The data presented here are in agreement with those of Mollison and Cutbush,[10] who found that of infants whose peak bilirubin concentrations reached approximately 30 mg. per 100 cc., kernicterus developed in about 50 per cent. Some infants with bilirubin concentrations as high as 40 mg. per 100 cc. escaped this complication, and in others with concentrations as low as 25 mg. or less, kernicterus developed. The authors concluded that there is no critical level of bilirubin associated with the development of kernicterus and suggested that a sigmoid curve would be obtained if the probability of kernicterus were plotted against the maximum bilirubin concentration.

Many problems remain unsolved. What is the nature of the pigment found in the brain of the infant with kernicterus? Is indirect bilirubin itself the agent that damages the brain, or is it perhaps some other product of red-cell breakdown? Is there a different "critical" point for serum bilirubin in a twenty-four-hour-old infant than in a forty-eight-hour-old infant? Is the "critical" level different in premature than in full-term infants? How long must bilirubin remain above a certain level before brain damage occurs? It is probable that most of these questions could be answered if daily serum bilirubin determinations, including one of umbilical-cord blood, were available in 100 babies with erythroblastosis not treated by exchange transfusions in whom kernicterus developed, in addition to an equal number who escaped kernicterus.

Until these questions are answered and until better criteria are available, it appears that serum bilirubin levels can serve as a valuable guide in the practical management of infants with erythroblastosis. The development of skin jaundice lags considerably behind the rise of serum bilirubin and cannot be relied upon as an indication of the bilirubin level in the first forty-eight hours of life. The discrepancy between skin jaundice and serum bilirubin in the infant with erythroblastosis becomes less marked in the third, fourth and fifth days of life.

Mollison and Walker[11] have recently demonstrated in controlled studies that exchange transfusion results in both higher survival rate and lower incidence of kernicterus in infants with erythroblastosis. Serum bilirubin levels are helpful in determining when exchange transfusions are needed in erythroblastotic babies who are more than twelve hours old. Cord-serum bilirubin levels are of relatively little value, however, so that the decision to do exchange transfusion at birth must depend on other criteria, as previously outlined.[12] We have in our hospitals attempted to keep the bilirubin

level below 20 mg. per 100 cc. in each case, doing multiple exchange transfusions if necessary. Although we have encountered no cases of kernicterus in over 200 consecutive cases of erythroblastosis treated according to this policy, it is still too early to be certain that such a level of serum bilirubin is safe.

Summary

Kernicterus is likely to occur in babies with serum bilirubin levels above 30 mg. per 100 cc. and unlikely to occur when the serum bilirubin remains below 20 mg. per 100 cc. Therefore, although it has not been proved that bilirubin is the actual cause of brain damage, tests of serum bilirubin in babies with erythroblastosis fetalis serve as extremely valuable guides to treatment.

By exchange transfusion, repeated if necessary, the serum bilirubin can be kept at relatively low levels, and kernicterus can be prevented.

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PHEOCHROMOCYTOMA WITH RUPTURE OF AN INTRACRANIAL ANEURYSM*

Report of a Case

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BOSTON

THE neurologic complications of pheochromocytoma have recently been emphasized by Apter and his associates,[1] who reviewed the literature and described a clinical case of their own. Out of approximately 200 cases of pheochromocytoma collected from the literature up to 1950, they were able to find 28 cases with evident neurologic complications, and in 16 of these the nervous system was examined at autopsy. The most common complication was intracranial hemorrhage, which occurred in 11 cases; in 2 of these the hemorrhages were subarachnoid. The origin of the subarachnoid hemorrhage, which was found in only 1 of these cases, was a ruptured saccular aneurysm.[2]

The following case report briefly describes the clinical and autopsy data of a patient who died of a ruptured intracranial saccular aneurysm associated with a pharmacologically active pheochromocytoma in whom it was possible to make the diagnosis clinically. The results of chemical analysis of the tumor and the relation of the pharmacologic activity of the tumor to rupture of the aneurysm are discussed.

Case Report

W. M., a 38-year-old Negro, was admitted to the hospital on August 14, 1951. One hour before entry he suddenly became apprehensive and restless and complained that he was going to have a stroke. He complained further of a frontal headache and vague abdominal pain. He then became unresponsive for 30 minutes. On recovery he thrashed about and stated that he was "going to die." He was confused and complained of stiff neck and generalized muscle pain.

For 10 years before admission the urine had occasionally been "smoky." During World War II he had been rejected for military service after physical examination on two occasions, without explanation.

One year before admission he consulted a physician because of nervousness and insomnia. At that time the blood pressure was 160/90. He was treated with aminophylline and sedatives, and on return visits the blood pressure had fallen to 140/90.

Physical examination showed a well developed, restless man who occasionally coughed up blood-tinged sputum. Examination of the lungs, heart and abdomen revealed no abnormality. On neurologic examination he was oriented but unable to recall any events of the hour prior to admission. The neck was stiff. The fundi showed narrowing of the arterioles, with compression of veins. The only abnormalities on examination of the cranial nerves were a decreased corneal reflex on the left and a slight weakness of the left lower facial nerve. Motor and sensory examination revealed no abnormality. The deep tendon reflexes were equal; the plantar reflexes were flexor.

The temperature was 99°F., by mouth, the pulse 52, and the respirations 20. The blood pressure was 128/92.

The urine, which was smoky in appearance, had a specific gravity of 1.011, and gave a +++ test for albumin and a + test for sugar. The sediment was loaded with red cells, and a few granular casts were present. The white-cell count was 14,500, with 76 per cent neutrophils, 18 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophils. The blood Hinton test was negative. The fasting blood sugar and blood urea nitrogen were within normal limits. There was no occult blood in the stool. The sickle-cell test was negative. Lumbar puncture revealed an initial spinal-fluid pressure equivalent to 400 mm. of water and a final pressure equivalent to 360 mm. The spinal fluid was bloody, with xanthochromic supernatant fluid. There were 1,860,000 red cells and 1900 white cells per cubic millimeter, of which 28 per cent were polymorphonuclear forms and the rest mononuclear cells. The total protein was 2400 mg. per 100 cc. Culture and Hinton tests of the spinal fluid were negative.

During the first 2 weeks of the hospital stay the patient was drowsy and anorexic. On the 3d day he complained that

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his head felt "like bursting." Examination showed a blood pressure of 168/102.

Between the 4th and 14th days he had continuous fever, the temperature ranging from 100 to 103°F. The systolic blood pressure varied between 192 and 116, and the diastolic between 115 and 74. The pulse was 70 to 80 per minute. Lumbar puncture done 11 days after admission showed an initial spinal-fluid pressure equivalent to 250 mm. of water and a final pressure equivalent to 175 mm.; the fluid was clear, with 12 red cells per cubic millimeter and a total protein of 28 mg. per 100 cc. By this time the hematuria and hemoptysis had cleared.

During the 3d week the patient was asymptomatic, without neurologic signs. Further investigations, including arteriography, were refused.

On the 21st hospital day he suddenly complained of a severe frontal headache; he was again restless and coughed up blood-tinged sputum. He became rigid and comatose. The reflexes were hyperactive, both plantar reflexes being extensor. Papilledema was noted in both fundi. The blood pressure was 185/115. Lumbar puncture showed a spinal-fluid pressure equivalent to 375 mm. of water, with grossly bloody fluid. The respirations became labored, and the patient died.

At autopsy the right adrenal gland was largely replaced by soft, encapsulated tumor measuring 5.0 by 6.4 by 4.0 cm. and weighing 72 gm. The periadrenal fat was discolored, being brown. A thin ridge of remaining adrenal tissue was recognizable along the medial border of the tumor. On cut section the tumor consisted of multilocular cysts containing dark-red, gelatinous material.

The left adrenal gland weighed 12 gm. The cortex contained a small adenoma measuring 1.5 cm. in diameter but in other respects was not unusual.

The heart weighed 460 gm. Right-sided dilatation and left-sided hypertrophy were present. The wall of the left ventricle measured 1.8 cm. The coronary arteries showed minimal atherosclerosis. The lungs were edematous. The kidneys were slightly congested.

The brain weighed 1540 gm. The subarachnoid space was filled with fresh blood. The right frontal lobe was swollen. The cerebral vessels were free of atheromatous thickening; at the junction of the anterior communicating and left anterior cerebral arteries there was an ovoid saccular aneurysm, which measured 0.5 by 0.4 mm. in diameter, with a tear on its medial surface. Small, unruptured saccular aneurysms were also present at the junction of the internal carotid and middle cerebral arteries bilaterally. Herniation of the hippocampal gyrus through the tentorial opening had occurred bilaterally.

Coronal sections revealed a meningocerebral hemorrhage into the right frontal lobe. There was edema of the right cerebral hemisphere, with subfalcial herniation and displacement of the ventricular system to the left. There were several secondary venous hemorrhages in the pons.

On microscopical examination the tumor had the typical histologic appearance of pheochromocytoma,[3] with large pleomorphic cells arranged in cords around thin-walled blood vessels. The tumor cells had eosinophilic cytoplasm and vesicular nuclei with prominent red nucleoli; some cells were multinucleated. Many cells contained granules of yellow-brown pigment in the cytoplasm. The pigment was argentophilic but did not stain for iron. Apart from the granules all the tumor cells showed a uniform brown coloring of the cytoplasm, which was also present in the intercellular ground substance and the periadrenal adipose tissue.

In the center of the tumor there was considerable hemorrhage and necrosis. Several arterioles within the tumor demonstrated intimal hyaline thickening.

Moderate atherosclerosis of the major coronary vessels was present in the heart. There was minimal fibrocaseous tuberculosis of the apexes of both lungs and edema and congestion of all lobes. Slight hemosiderosis of the renal tubules was evident. There were occasional hyalinized arterioles but no glomerular fibrosis.

The subarachnoid space over the right frontal lobe of the brain showed well preserved red blood cells. In the midline of the brachium and tegmentum pontis several small perivenous hemorrhages were present. The ruptured aneurysm appeared as an outpouch of the anterior communicating artery in which both the elastic membrane and muscular coats were deficient. There was no other cerebral-artery disease.

On chemical analysis of the pheochromocytoma,* by paper-partition chromatography and a modification of von Euler's colorimetric method, the tumor was found to contain 1.57 mg. per gram of nor-epinephrine and 1.8 mg. per gram of epinephrine For the entire adrenal tumor the total content of nor-epinephrine was calculated to be 113 mg. and that of epinephrine 129.6 mg.

Discussion

The chemical analysis of the tumor was similar to others that have been reported. It contained 113 mg. of nor-epinephrine and 129.6 mg. of epinephrine, which is 46 per cent of nor-epinephrine. In man, the normal adrenal glands contain 2.4 to 4.0 mg. of epinephrine,[4] 10 to 30 per cent of which is nor-epinephrine.[5] Pheochromocytomas may contain 14 to 90 per cent of nor-epinephrine.[5]

Both epinephrine and nor-epinephrine raise the systolic blood pressure and in high dosage cause peripheral constriction.[5] Recently, the effects of intravenous infusion of epinephrine and nor-epinephrine on cerebral circulation and metabolism have been studied in man.[6] Epinephrine increases cerebral blood flow and metabolism, together with the rise of arterial blood pressure, but does not alter cerebrovascular resistance. Nor-epinephrine is reported to lower cerebral blood flow without alteration of cerebral metabolism despite a marked rise in mean arterial blood pressure, apparently owing to an increase in cerebrovascular resistance, a situation similar to that seen in severe essential hypertension.

The nature of the constriction of retinal and cerebral arterioles in hypertensive encephalopathy and allied disorders such as pheochromocytoma has recently been discussed by Denny-Brown.[7] In such disorders vascular constriction appears to affect the smaller cerebral vessels.

In view of the visible constriction of the retinal arterioles and the high nor-epinephrine content of the pheochromocytoma present in the case reported above, it seems likely that during the paroxysmal bouts of hypertension constriction of smaller cerebral vessels occurred. Such a situation would elevate further the pressures within the larger cerebral vessels and favor rupture of a saccular aneurysm, with its associated defect of muscle coat and elastic membrane.

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*Kindly performed by Dr. Marcel Goldenberg, of Columbia University College of Physicians and Surgeons.

ANGINA PECTORIS ASSOCIATED WITH VENTRICULAR BIGEMINY, CONTROLLED BY PROCAINE AMIDE

Report of a Case

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THE occurrence of premature ventricular beats during an attack of angina pectoris was first demonstrated by Mackenzie[1] with pulse tracings and by Goldhammer and Scherf[2] electrocardiographically. Proger, Minnich and Magendantz,[3] in a study of the circulatory response of patients with angina pectoris to exercise, showed that one group developed premature beats during attacks and that attacks could be abolished and the exercise tolerance increased by quinidine. This action of quinidine was confirmed by Riseman and Brown,[4] who further established the value of this drug in a large group of patients with angina pectoris. In 1948 Porter[5] reported 4 cases of this condition in which attacks were associated with bigeminy and controlled by quinidine.

The patient in the case reported below likewise gave a history of typical angina pectoris. Attacks were precipitated by specific degrees of exertion and occasionally by excitement. On the two-step exercise-tolerance test, substernal pain regularly developed after 29 to 31 trips. Pain appeared with the onset of premature beats in bigeminal rhythm and was relieved when this rhythm terminated. Attacks were controlled initially by quinidine and during the past sixteen months by procaine amide hydrochloride.

CASE REPORT

R. M., a 50-year-old building inspector, first seen on January 18, 1951, gave a history of attacks of severe substernal distress of 3 weeks' duration. The first attack occurred while he was walking across a plant during an inspection. Severe pain started in the epigastrium and radiated up to either side of the sternum. Forced to stop, he was immediately relieved, but mild distress continued for 2 or 3 minutes. A similar attack occurred a day later while he was walking up a hill. During the next few days he had several attacks, which were somewhat shorter in duration, always precipitated by walking and relieved by rest. The past history was not remarkable.

Examination of the eye grounds showed no arterial narrowing. The heart was not enlarged. The sounds were slow and regular, and there were no murmurs. The blood pressure was 120/80. An electrocardiogram taken with the patient resting was normal.

A 2-step exercise-tolerance test was performed with an ice cube held in the left hand.[6] He complained of substernal distress and tightness in the neck on the 29th trip. At this moment bigeminal rhythm was noted by pulse and auscultation. Exercise was then resumed to 32 trips without any appreciable increase in pain. After reclining, substernal tightness and a choking sensation continued; during this time the electrocardiogram showed a bigeminal rhythm with noninterpolated premature beats that did not alter the dominant rhythm. The sinus rate was 60. The ST interval was depressed in Lead V_4 (0.2 second). There were no changes in the standard leads. After 2 minutes bigeminy gave way to premature beats occurring every 3 to 5 cycles and simultaneously he noted a decided relief of pain. Two and a half minutes later premature beats entirely disappeared and at this moment he volunteered the information that neck tightness had left him.

One week later an attack occurred on the 31st trip. Auscultation revealed bigeminy with a dominant sinus rate of 65. The patient complained of a squeezing pain in the middle and upper sternal regions. Bigeminy continued for 2 minutes and 45 seconds, after which premature beats became less frequent, and a few seconds later, normal rhythm was established. Severe pain ceased with the termination of bigeminy, and mild pain continued until all premature beats had disappeared. He was then given 0.4 gm. of quinidine by mouth on an empty stomach, and 1½ hours later he went 42 trips without pain or the appearance of premature beats. Quinidine in a dosage of 0.2 gm. 3 times a day was prescribed.

Two weeks after the 1st interview, he reported a severe attack in the course of walking that forced him to stop. This attack persisted for approximately 3 minutes. In addition he had 3 mild attacks, lasting a few seconds, that were precipitated by emotional excitement. Quinidine had been discontinued because of diarrhea. On the exercise-tolerance test a typical attack occurred after 27 trips. Its onset and cessation, as before, were simultaneous with premature beats and bigeminal rhythm. Procaine amide, 0.25 gm., was then given, and 45 minutes later a second test performed. This time the patient went 46 trips without pain or premature beats. He was then put on a program of procaine amide, 0.25 gm. every 4 hours.

A week later, 3½ to 4 hours after taking 0.25 gm. of procaine amide, he had an attack after 40 trips. This was again associated with a bigeminal rhythm, which lasted 2½ minutes, the substernal distress disappearing with the cessation of the premature beats. During the next 6 weeks there was no recurrence of attacks on procaine amide, 0.25 gm. every 4 hours, in spite of moderate activity. On an exercise-tolerance test, after this period, he went 50 trips without a typical attack. After 30 trips, however, he noted the onset of mild discomfort over the upper portion of the chest and the neck region, and at this point premature beats appeared every 4th or 5th cycle. This continued up to 50 trips and for 30 seconds after reclining.

When last examined 16 months after onset he reported no recurrences in spite of excessive activity. Two months before, he omitted procaine amide and found that his capacity for exercise was unchanged and attacks did not recur. On an exercise-tolerance test he went 50 trips with no pain or premature beats. At the end of the test his pulse was 100, and he showed considerably less dyspnea than is usual with this degree of exertion.

DISCUSSION

The association of attacks of angina pectoris with premature beats is probably more common than is evident from the literature. This patient complained only of pain. After the attacks were precipitated by exercise, however, he noted and recalled the presence of palpitation with most of his attacks. Careful inquiry in other patients may bring out the association and make the diagnosis suggestive from the history alone.

The value of the exercise-tolerance test is evident, for without direct observation the exact mechanism could not be established and proper therapy employed. The two-step exercise-tolerance test

was carried out with an ice cube held in the left hand according to the suggestion of Freedberg, Spiegl and Riseman.[6] Table 1 summarizes the results in the case reported above. The attacks occurred regularly after 27 to 31 trips. In all attacks severe pain appeared with onset of bigeminy and continued up to its cessation. Thereafter occasional premature beats occurred for a short period, during which there was mild discomfort.

The association of angina pectoris and premature beats does not permit one to say whether myocardial ischemia leads to the irregularity or whether the premature beats precipitate the ischemia. Both quinidine and procaine amide act to suppress premature beats. The action of quinidine in the prevention of attacks of angina pectoris is not clear. Since it is not a vasodilator, it probably acts directly in the manner of quinine in the abolition of leg cramps.

Porter[5] noted a poor prognosis in his patients with angina pectoris and bigeminy. This prognosis is primarily related to the presence of advanced coronary-artery disease, which must likewise be considered in the case reported above, although sixteen months after onset the patient was free of attacks. There is also the possibility that the poor prognosis is related to the precipitation of ventricular fibrillation and sudden death during anginal attacks with bigeminy.

TABLE 1. *Results of Two-Step Exercise Test Before and After Medication.*

DATE	MEDICATION	NO. OF TRIPS	DURATION OF SEVERE CHEST PAIN	DURATION OF BIGEMINY	TOTAL DURATION OF PAIN	TOTAL DURATION OF PREMATURE BEATS
			min.	min.	min.	min.
1/18/51	None	29	2	2	4½	4½
1/25/51	None	31	2¾	2¾	3	3
1/25/51	Quinidine	42	0	0	0	0
2/4/51	None	27	1	1	1¼	1¼
2/4/51	Procaine	46	0	0	0	0
2/13/51	Procaine	40	2½	2½	2½	2½
3/26/51	Procaine	50	0	0	Mild pain with premature beats every 4th or 5th cycle from 30th to 50th trip	
4/14/52	None	50	0	0	0	0

SUMMARY

A case of angina pectoris associated with bigeminy and premature ventricular beats is reported. This specific form of angina pectoris was successfully controlled by procaine amide. The significance of this case is discussed.

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MEDICAL PROGRESS

THE BLOOD VOLUME IN VARIOUS MEDICAL AND SURGICAL CONDITIONS*

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AMONG the quantitative blood examinations frequently used in health and in abnormal states are the red-cell count and the hematocrit. Rarely in routine medical practice does the physician or surgeon determine the total red-cell volume and plasma volume. We have had extensive experience with blood-volume determination, and from the evidence presented in this paper conclude that red-cell counts are often misleading and that the determination of the blood volume turns out to be of great importance in the handling of major medical and surgical problems.

Since the original description of the method by Hevesy and Zerahn[1] of the in vitro labeling of red blood cells with radioactive phosphorus (P^{32}), there have been a number of reports on the determination of the blood volume by this method[2-6]; however, only a few of these reports were concerned with a specific clinical state.[7-11] The superiority of this method for blood-volume determination has been previously reported.[12, 13] A modification has been used in this laboratory in experimental studies on animals[14] and in studies on patients with various clinical conditions. Rather than review the literature on the various pathologic states discussed, we shall try to present the salient features in each section.

METHODS

In all the studies reported here, the blood volume was determined with P^{32}-labeled red cells; 15 cc. of blood is withdrawn from an antecubital vein into a heparinized syringe, and 5 cc. is placed in a sterile, rubber-capped, centrifuge tube and incubated at 37°C. with constant rotation with ½ mc. of radioactive phosphorus in the form of isotonic sodium dihydrogen phosphate at a pH of 7.3. At the end of two hours about 50 per cent of the radiophosphate has been incorporated into the phosphorus-containing compounds of the red cells. The red cells are then washed three times with saline solution and resuspended in the patient's own plasma. One cubic centimeter of the reconstituted blood is then injected into the patient, and with the same syringe and needle, 1 cc. is placed in a 2000-cc. flask. At the end of fifteen minutes, blood is withdrawn from the opposite arm of the patient with a minimum of stasis, and 5 cc. is placed in a dry oxalate tube. Fifteen minutes is allowed for mixing within the patient, since this period has been shown to be sufficient. Furthermore, during this time less than 1 per cent of the labeled phosphorus will be lost from the red cells. This is too small a quantity to be measured precisely. The blood samples and the standard are then counted in the following manner: 0.1 cc. is placed on a small piece of filter paper on an aluminum foil, which is then dried, wrapped in cellophane and placed around a 1 B–85 thyrode, Geiger-Müller tube. With knowledge of the amount of radiophosphorus injected from the standard and the amount of radiophosphorus per cubic centimeter of the patient's blood, it is easy to calculate the total red-cell volume from the formula

$$TRCV = \frac{\text{cpm/0.1 cc. Std.} \times 2000 \times \text{Hematocrit}}{\text{cpm/0.1 cc. blood}}$$

The blood volume is calculated from the equation $BV = \frac{TRCV}{\text{Hematocrit}}$. The plasma volume is obtained from the difference of the blood volume and the total red-cell volume. Figure 1 shows the equipment, which is strong, simple to use and easily introduced into the routine of any small or large clinical laboratory.

GENERAL CONSIDERATIONS

This method is reproducible; in a series of 24 repeat blood-volume determinations, the greatest deviation found was 761 cc. (7.4 per cent), and the average variation was 266 cc. (5.7 per cent). No significant difference in the blood volume of the rat was found when P^{32}-labeled red cells were compared with Fe^{59}-labeled cells, confirming the fact that P^{32} is a satisfactory labeling agent for the red cell for blood-volume determinations.[14] We have usually found it convenient to express the blood volume in terms of cubic centimeters per kilogram of body weight, since this permits a more satisfactory comparison between different persons.

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Normal Values

Blood-volume values for normal adults are shown in Table 1. The figures for the 71 male subjects are derived from 59 cases reported in the literature and 12 cases from this laboratory.[15] The figures for the 16 female subjects are from this laboratory[16] and have recently been confirmed.[17]

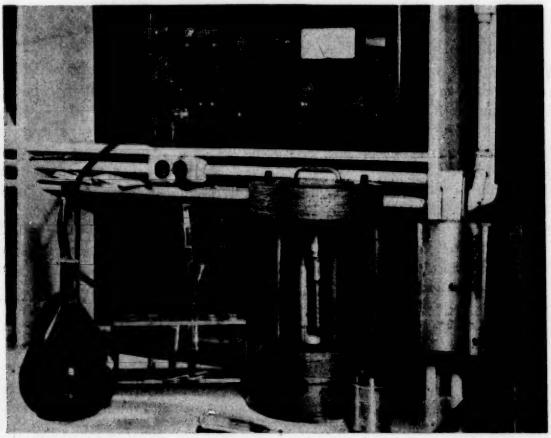

FIGURE 1. *Equipment for Determining Blood Volume with the Use of P^{32}-Labeled Cells.*

Congestive Heart Failure

With but one exception[18] the blood volume in congestive heart failure as measured by the dye methods has been reported to be elevated.[19-24] The patients observed by us have been divided into two groups (See Table 2),[13] as follows:

Group I. This group included patients in whom the blood volume was normal, and Group II those in whom the blood volume, total red-cell volume or plasma volume was elevated. The latter group has again been subdivided into two groups: those who had rheumatic heart disease, and those who did not have rheumatic heart disease. As Table 2 shows, 12 of the 26 patients had blood volumes that were in the normal range or low normal. Eleven of these patients were in heart failure as a result of arteriosclerotic or hypertensive cardiovascular disease; 1 patient in this group had rheumatic heart disease. Phlebotomy had been performed in 1 case approximately a week before the blood-volume determination.

Group II. The 7 patients with rheumatic heart disease had blood volumes, total red-cell volumes and plasma volumes considerably elevated but had normal hematocrits.

The second subgroup of Group II comprised 8 patients with arteriosclerotic or hypertensive heart disease. The average total red-cell volume was normal in this group, but the average plasma volume for the group was at the upper limit of normal. Thus, the average hematocrit was low. The average total blood volume in this group was slightly increased, as compared to normal values. Therefore, the typical blood-volume picture in congestive heart failure can

TABLE 1. *Blood Volumes in Normal Male and Female Subjects.*

Subjects	No. of Cases	Blood Volume	Total Red-Cell Volume	Plasma Volume	Hematocrit
		cc./kg.	*cc./kg.*	*cc./kg.*	%
Males	71	69.0	29.9	38.7	43.0
Females	16	64.4	27.0	37.0	42.0

TABLE 2. *Blood Volume in Congestive Heart Failure.*

Group	No. of Cases	Blood Volume	Total Red-Cell Volume	Plasma Volume	Hematocrit
		cc./kg.	*cc./kg.*	*cc./kg.*	%
I	12	54.7	26.7	27.5	48.8
II A	7	88.7	41.1	47.1	46.4
B	8	73.4	26.0	46.8	35.4

be described in terms of etiology. When failure was a result of long-standing rheumatic heart disease, the blood volume was almost uniformly elevated, whereas in patients with failure developing from arteriosclerotic or hypertensive cardiovascular disease, the blood volume was low, normal or, at most, slightly elevated. Repeat studies of the blood volume in 5 patients in Group I demonstrated that as these patients became compensated, the blood volume increased. In 1 patient with rheumatic heart disease, the blood volume showed an insignificant decrease as compensation occurred. These findings seem to require some revision of the classic concept of the increased blood volume in congestive heart failure. They are surprising, in that with congestive heart failure, the physician sees the patient with engorged vessels and tissues full of blood. The arterial side may provide blood for the venous side of the circulation in congestive heart failure. In partial agreement with the present findings are the studies of Nylin and his co-workers,[9] who found a normal blood volume in left-sided and an elevated volume in right-sided heart failure, and those of Ross and his associates,[10] who found the volume to be normal.

Uremia

Although anemia is a well known complication of uremia, there are few reports of the blood volume in this condition.[25, 26] In 14 patients with blood urea nitrogen levels ranging from 30 to 240 mg. per 100 cc. and associated with hypertension in 6 cases, chronic nephritis in 4 cases and lower-nephron nephrosis, amyloidosis of the kidney with diabetes and lupus and of unknown cause in 1 patient each, the blood volume averaged 54.3 cc. per kilogram of body weight, with a range of 34.3-74.8 cc.; the total red-cell volume averaged 14.3 cc. per kilogram of body weight and varied from 7.9 to 22.9 cc., and the plasma volume averaged 39.6 cc. per kilogram, with a range of 22.4 to 60.5 cc. The average plasma volume is misleading, because 4 patients had plasma volumes below, and 4 volumes above normal. It is of interest to note that the lowest blood volumes observed were in this group of patients. Thus, in uremia the picture seems to be a general decrease in the red-cell volume, and in half the patients no change in the plasma volume. The red-cell count and hematocrit, therefore, do not give a true picture of the total red-cell volume.

Pulmonary Tuberculosis

With the use of T-1824 it has been found that the blood volume was reduced 15 per cent in pulmonary tuberculosis.[27, 28] Table 3 shows that in our series of 24 patients (14 female and 10 male) there was a distinct decrease in the total blood volume. Since the total red-cell and plasma volume fell to an equal degree, there was little and certainly no significant change in the hematocrit.[29] Thus, in this group of patients a normal red-cell count or hematocrit is misleading since it does not mean a normal oxygen-carrying power of the blood. In this connection it is interesting that 16 of the patients were candidates for thoracic surgery and all had active pulmonary tuberculosis. The fallacy of relying on the red-cell count or hematocrit as a measure of oxygen-carrying power is evident.

Table 3. *Blood Volume in Pulmonary Tuberculosis.*

Subjects	No. of Cases	Blood Volume	Total Red-Cell Volume	Plasma Volume	Hematocrit
		cc./kg.	cc./kg.	cc./kg.	%
Males	10	60.6	26.2	34.0	43.2
Females	14	53.5	22.0	31.1	40.9

Cirrhosis

Studies with the conventional dye methods in this disease have shown almost uniformly a large plasma volume resulting in an elevated blood volume.[30-32] Some workers have stated that this dilution of the blood causes the red-cell counts to be low, and the anemia is thus relative.[32]

Table 4 shows that revision of such an interpretation is necessary.[33] The results were divided into four groups: Group I, subjects in whom the plasma volume was pathologically low; Group II, those in whom the value was a low normal; Group III, those in whom the volume was pathologically high; and Group IV, those in whom the value was a high normal. Table 4 shows the averages of the blood volumes, total red-cell volumes and plasma volumes of all the groups. In all four groups it is seen that the total red-cell volume was low. These patients were definitely anemic. There was some correlation between plasma volume and total red-cell volume. The two groups having the higher plasma volumes had significantly higher total red-cell volumes.

Table 4. *Blood Volume in Portal Cirrhosis.*

Group	No. of Cases	Blood Volume	Total Red-Cell Volume	Plasma Volume	Hematocrit
		cc./kg.	cc./kg.	cc./kg.	%
I	7	43.6	16.8	26.4	38.2
II	7	50.9	17.2	33.4	33.7
III	7	77.0	20.4	56.1	26.4
IV	7	65.1	22.3	42.1	34.0

Table 5 presents a serial study of the blood volume in a patient undergoing therapy with significant clinical improvement. This shows a progressive increase in the plasma volume and little or no change in the total red-cell volume. The lack of correlation

between the total red-cell volume and the hematocrit in this patient should be noted. In still another patient in whom the first blood volume was done as the patient was leaving the hospital after a course of therapy, a normal blood volume was found. This patient then went home and back to her prior alcoholic intake. She later came back to the hospital with a very low total red-cell and low plasma volume.

TABLE 5. *Serial Blood-Volume Studies in a Case of Portal Cirrhosis.*

DATE	BLOOD VOLUME	TOTAL RED-CELL VOLUME	PLASMA VOLUME	HEMATOCRIT
	cc.	*cc.*	*cc.*	*%*
5-16-50	2600	1010	1580	39.0
6-13-50	2930	910	1960	31.6
9-19-50	3150	1050	2140	33.0

CANCER

Most physicians think of advanced cancer as being associated with more or less severe anemia, as determined by red-cell counts and hematocrit. There are, however, only two reports dealing with blood volume in cancer, and the data at present are conflicting. Clark and his co-workers[34] found with T-1824 that there was a reduction in the blood volume that was due principally to a reduction in the total red-cell volume, whereas Bateman[35] reported the blood volume to be variable. Shen and Homburger[36] have recently reviewed the theories and evidence for the various mechanisms, particularly the invasion of the bone marrow, that have been postulated for the development of anemia in their patients, concluding that the anemia is not usually due to invasion of the bone marrow. There still remains to be settled the question of what percentage of these patients are really anemic in terms of total oxygen-carrying capacity, rather than in terms of the concentration of red cells in the peripheral blood. In our studies of 63 patients with different tumors 22 (35 per cent) had total red-cell volumes less than 24 cc. per kilogram of body weight, which we consider to be the lower level of normal.[37] The following groups were studied: pancreas, breast, lung, gastrointestinal tract and a miscellaneous group.

Six patients with cancer of the pancreas were studied, none of whom are still living. There was only 1 patient who was anemic by blood-volume standards and who died of his disease a month after the blood volume had been determined. There were 5 nonanemic patients, who died one to seven months after determination of the blood volume.

Seven patients with cancer of the breast were studied; 3 were anemic, and 4 were not. Of the 3 anemic patients, 2 were living, seven and eight months after the blood-volume determination, and 1 was dead four months after the determination. Of the 4 nonanemic patients, 3 were living three to eleven months and 1 died of the disease three weeks after the blood-volume determination.

Eleven patients with pulmonary cancer were studied, of whom 4 were anemic, and all 4 are dead; within two to six weeks, 3 patients succumbed to this disease, and 1 died ten months later after an operation. Of the 7 nonanemic patients 5 died after two weeks to four months, and 2 were living at thirteen and fifteen months.

Twenty-two patients with carcinoma of the gastrointestinal tract were studied, 6 of whom were anemic. Of these, 3 were living after two to five months, and 3 died within three weeks (2 of these died postoperatively). Of the nonanemic patients, 7 were living two months to one year after the blood-volume determination, and 9 died one month to six months later; 3 died of postoperative complications, and the other 6 of the disease.

Of 17 patients with miscellaneous cancers, 8 were anemic and of these, 1 died at four months, and 7 were living three to twenty-two months later. Of the nonanemic patients, 4 died within one to three months of the beginning of the disease, and 5 survived.

Of these 63 patients it is seen that in the anemic and the nonanemic groups the mortality has been about the same. In each group approximately half the patients died after their blood volume was determined. Thus, the anemia of cancer is inconstant and occurs in only a fraction of the cases. Since none of these cases were followed completely with repeated blood-volume determinations, it is not possible to say in which of the nonanemic patients anemia developed during the course of the disease. However, the large number of patients who were not anemic at the time of the blood-volume determination and succumbed to the disease within a short period, less than a few months, indicates that many of these patients were not anemic at the time of death.

LEUKEMIA

There are only a few reports on the blood volume in leukemia as determined by the dye methods.[38-40] In general an increase in the blood volume has been reported to be due to an increase in the plasma volume in patients with chronic myelogenous and lymphatic leukemia who had palpable spleens. Figure 2 presents the findings in our patients with chronic leukemia.[15] The ellipse* represents the area in which 92 per cent of normal values will fall. This figure demonstrates that in leukemia the total red-cell volume cannot be predicted from the hematocrit or red-cell count and vice versa. The region where the hematocrit lies between 20 and 35 and

*Calculated by the method of Smith,[41] as corrected.[42]

where the total red-cell volume is above 20 cc. per kilogram of body weight is filled almost entirely with patients with chronic myelogenous leukemia, all but 1 of whom had palpable spleens. Thus, when the spleen is palpable, the hematocrit may be low, because the plasma volume is pathologically large. This is a relative anemia, but

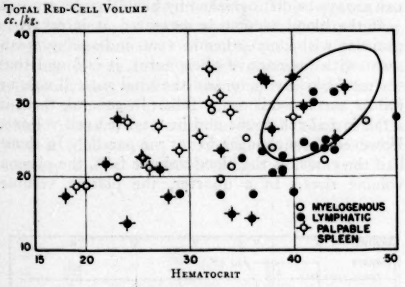

FIGURE 2. *Blood Volume in Chronic Leukemia.*

actually these patients are only mildly anemic in terms of total oxygen-carrying capacity. In other studies it has been shown that the anemia of leukemia is not myelophthisic, but is associated with a greater than normal rate of red-cell production.[43] The anemia is due to a shorter than normal red-

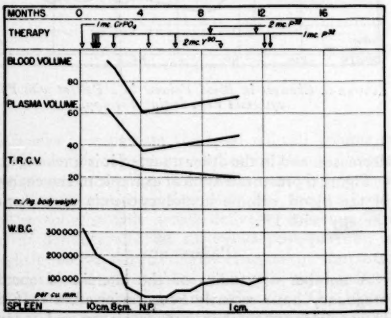

FIGURE 3. *Serial Study of Changes in Blood Volume in a Patient with Chronic Myelogenous Leukemia.*

cell life, occurring regularly in patients with leukemia.[44-47] In patients with chronic lymphatic leukemia there is no correlation between splenomegaly and a high plasma volume. On the other hand it is not unusual to observe abnormally high plasma volumes in chronic lymphatic leukemia.

Repeat blood-volume studies in chronic myelogenous leukemia during treatment show that (Fig. 3) as the white-cell count falls and the spleen decreases in size, there is a remarkable lowering of the blood volume, owing almost exclusively to a large decrease in the plasma volume. At the same time there is a small decrease in the total red-cell volume. As the white-cell count later rises, the spleen again becomes palpable, and the plasma volume increases. In this connection it is interesting that the plasma proteins remain near normal, even though the plasma volume is so much increased. Here is another example of the unreliability of the measurement of the plasma concentration of a substance such as plasma protein. In many patients with leukemia, when the plasma volume is high there may be a twofold increase in total plasma protein, but a normal plasma protein concentration. In patients with chronic lymphatic leukemia such striking changes in the blood volume

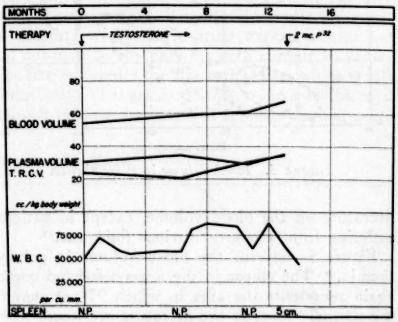

FIGURE 4. *Serial Study of Changes in Blood Volume in a Patient with Chronic Lymphatic Leukemia.*

have not been observed. In a few patients treated with testosterone, we have observed significant increases in the total red-cell volume, as shown in Figure 4. However, it should be noted that as the spleen became larger the plasma volume increased, and thus the total blood volume also increased.

POLYCYTHEMIA

As measured with the dye methods the blood volume has been found to be elevated in polycythemia vera.[40, 48-51] In general, with the T-1824 and red-dye methods, most observers have found that the average blood volume for a given series was approximately 160 cc. per kilogram of body weight. This is much greater than the 78.7 cc. per kilogram of body weight that we have found in a series of 32 patients with hematocrits of 55 per cent or higher. The one exception is the case reported by Haden,[51] in which the average was much less, being 106 cc. per kilogram of body weight. This elevation of

blood volume found with the dye method holds for both secondary and primary polycythemia, although Haden inferred from his determinations that in polycythemia vera there was a relatively greater increase in the total red-cell volume than in patients with secondary polycythemia.[51-54] Relative polycythemia, in which there is a normal total red-cell volume but a pathologically low plasma volume resulting in a falsely high red-cell count and hematocrit, has been unrecognized in the

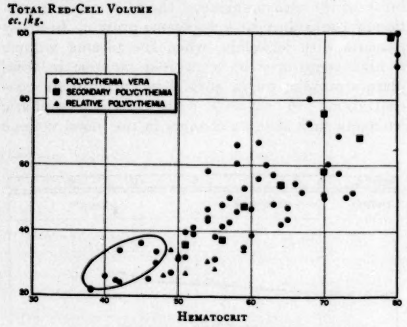

FIGURE 5. *Blood Volume in Polycythemia.*

literature on the blood volume, except in patients suffering from shock or obvious fluid loss.[55]

Figure 5 concerns the blood volume in polycythemia.[56] The ellipse in the lower left-hand corner again represents the area in which 92 per cent of the normal values in the literature are found when the labeled-cell method has been used. Several points are brought out in this figure. The first is the great variation of total red-cell volume for a given hematocrit. The second is that patients with secondary polycythemia cannot be separated from patients with polycythemia vera by blood volume, both having similar elevations in total red-cell volume and a decrease in plasma volume. In all but 1 patient with hematocrits of 55 per cent or higher, the plasma volume was below the average for normal; and of these, three fourths are below the lower limit for normal. Thus, in both polycythemia vera and secondary polycythemia the characteristic picture is an elevated total red-cell volume and a low plasma volume. However, in relative polycythemia the total red-cell volume is normal, but the hematocrit is elevated, owing to a very low plasma volume. These patients were referred to us with a diagnosis of polycythemia vera. Previously, this picture has been recognized only in patients with dehydration or in shock. We have recently described two causes of this picture — the first in the early periods of altitude acclimatization[57] and the second in a group of patients at sea level.[55] The etiology is obscure in the latter group; it may be of psychosomatic origin, representing an effect of psychic stress rather than the anoxic stress of the first group. Thus, blood-volume determination permits the separation of patients with absolute polycythemia from those with relative polycythemia but does not permit the differentiation of primary and secondary polycythemia, which can always be distinguished by blood oxygen studies.

If the blood volume is measured at intervals in patients with polycythemia vera undergoing treatment with radioactive phosphorus, it is found that the total blood volume and the total red-cell volume fall as the red-cell count falls. In general, there is a fall in red-cell count and in total red-cell volume. However, these changes do not run parallel. In about half the cases, as the blood volume falls, the plasma volume rises. In a quarter, the plasma volume

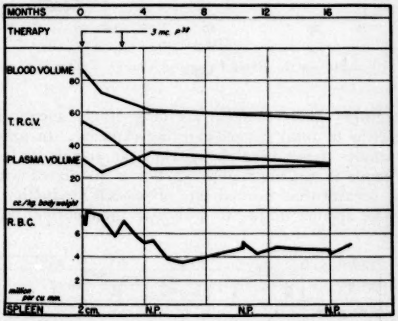

FIGURE 6. *Changes in Blood Volume in a Patient with Polycythemia Vera during Therapy.*

decreases, and in the other quarter, it is unchanged.[58]

Figure 6 presents a typical example of the changes of the blood volume in polycythemia vera during therapy with P^{32}.

PREGNANCY

A number of studies of the anemia of normal pregnancy have recently been reviewed.[59-62] If the obviously nutritional or iron-deficiency and macrocytic anemias of pregnancy are excluded from discussion, it has been well demonstrated that in normal women the concentration of red cells and hemoglobin progressively decreases, reaching a minimum in the last trimester of pregnancy, and that in the last month the concentration of red cells and hemoglobin in the peripheral blood rises. Studies of the blood volume with T-1824[62] and radioiron-labeled red cells[61] have shown a progressive increase in both, the total red-cell volume and plasma volume, the plasma volume rising much more than the

total red-cell volume. These studies indicate that this anemia is partly relative. Studies in this laboratory showing that there is a real anemia during pregnancy are based on two groups of patients, the first comprising 62 patients seen in the first and second trimesters in private practice and the second 117 patients seen in the second and third trimesters in the obstetric service of the Highland-Alameda County Hospital. From this study it is apparent that, as compared to normal nonpregnant women, pregnant women disclose a distinct and significant decrease in the total red-cell volume in the first trimester, the value reaching a minimum in the second month of pregnancy and thereafter slowly rising to reach a maximum in the ninth month. This is followed by a significant decrease before delivery and a 300-cc. decrease at delivery. At

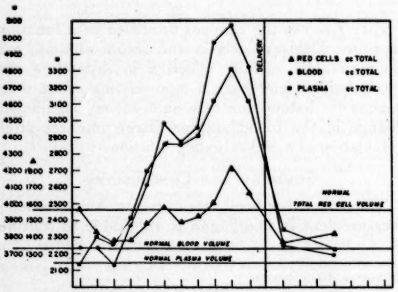

FIGURE 7. *Blood Volume in Pregnancy.*

six weeks post partum the total red-cell volume is still below normal. In our studies the plasma volume begins to increase in the second month and reaches a maximum at the ninth month; like the total red-cell volume, it falls before delivery, decreases 700 cc. at delivery and, at six weeks post partum, is slightly above normal. The changes in the total blood volume reflect these changes in total red-cell volume and plasma volume (Fig. 7). The blood-volume decrease at delivery is approximately 1000 cc. This has been repeatedly observed with blood-volume studies but is much larger than can be accounted for by external loss.[60] The basis for the discrepancy is obscure. The close agreement between the values obtained in our two different groups in the overlap period of second trimester was sufficiently good to justify our considering these patients as one group. These patients were all given the usual prenatal care, including oral supplements of iron. It is difficult to state whether this would affect the total red-cell volume. However, the agreement between our data and those of Caton and his co-workers,[61] whose patients did not receive supplemental iron, is such that little or no effect of the additional iron could be noted by comparison of the two groups of patients.

Decreases in the plasma volume in pre-eclampsia were noted by Dieckman[63] and by Freis and Kenny.[64] In the course of our studies 8 women were seen who were pre-eclamptic, and, in these, the blood volume was found to be remarkably decreased, largely because of fall in the plasma volume, although a decrease in the total red-cell volume was also noted. These women were definitely oligemic and anemic as compared to other pregnant women in the third trimester of pregnancy.

Plasma Volume

Figure 8 shows the plasma volume and the total red-cell volume for a group of 63 patients in whom the total red-cell volume was below 20 cc. per kilogram of body weight. This was an unselected group of patients with anemia from various causes but did not include any patients with chronic leukemia. The line represents the theoretical line, which would describe the changes in plasma volume as the total red-cell volume decreased, if for every cubic centi-

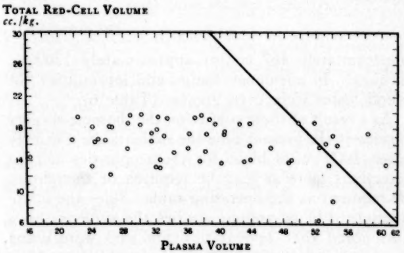

FIGURE 8. *Plasma Volume in Anemia.*

meter of decrease in total red-cell volume there was a corresponding cubic-centimeter increase in plasma volume, thus maintaining a constant blood volume. As can be seen from this figure such a correlation does not exist. In anemia there is no constant reciprocal relation between total red-cell volume and plasma volume such as Gibson et al.[48] have reported. This is unlike the situation holding in polycythemia.[56]

Thoracic Surgery

Allbritten and his co-workers,[27] using T-1824, found that in a thoracoplasty the blood loss was approximately 700 cc. In patients with pulmonary tuberculosis and in a few patients with other surgical conditions of the thorax, the blood volume was determined two to six days before and two to four

days after surgery.[12] From the preoperative and postoperative blood volumes and the amount of blood and plasma transfused, the amount of blood, red cells and plasma lost could be calculated. Table 6 shows the average blood loss in 24 patients. In 4 patients undergoing a first-stage thoracoplasty, the blood loss varied from 350 to 1500 cc.; the red-cell loss in 2 patients was unusual. This arises in the following manner: transfusions in the period of active blood loss were probably inadequate, and so, to compensate for the blood-volume loss, fluid entered the circulatory system from interstitial spaces and total body water to make up this volume deficit. Therefore, the net plasma-volume loss in these patients was not equivalent to an amount of plasma that would be required by the volume of red cells lost. In a similar manner the blood losses in the second stage of thoracoplasties are shown. In 12 thoracoplasties, the average red-cell loss was approximately 467 cc., or approximately 1200 cc. of blood. In pneumonectomies and lobectomies the blood losses were even greater (Table 6).

TABLE 6. *Blood, Red-Cell and Plasma Loss in Thoracic Surgery.*

OPERATION	NO. OF CASES	BLOOD LOSS	RED-CELL LOSS	PLASMA LOSS
		cc.	cc.	cc.
Thoracoplasty	12	910	467	468
Pneumonectomy	4	2840	1267	1603
Lobectomy	8	2680	1156	1628

As a result of these studies on the thoracic-surgery service at the present time the patients are routinely given 1000 cc. of blood for thoracoplasties and for resections more as may be required or thought to be required at the operating table. Since the introduction of blood-volume studies the surgeons have also noted that several patients who were doing poorly postoperatively had low volumes. After transfusions these patients showed considerable clinical improvement. In general this service has noted that more blood is being used and that it is used quantitatively in the sense that the surgeons can judge better how much blood is needed preoperatively and postoperatively and are achieving better postoperative care and results.

General Surgery

Bonica and Lyter[65] have recently summarized much of the pertinent literature on blood loss in general surgery. Table 7 shows the average blood-volume, total red-cell-volume and plasma-volume loss in various surgical procedures studied by us. This demonstrates that in most major surgical procedures total red-cell-volume loss was about 400 cc. This implies a blood-volume loss of about 1000 cc. However, there is great variation from patient to patient for any given procedure.

Effect of Plasma-Volume Expanders on Blood Volume

To study the effect of various plasma-volume expanders, the blood volume was determined in a group of subjects. Then the changes in blood volume produced by dextran (500 cc., or 6 per cent), gelatin (500 cc., or 5 per cent), plasma (500 cc.) and serum albumin (100 cc. concentrated) were determined by a method utilizing the change in the amount of P^{32} per cubic centimeter of blood.[66]

TABLE 7. *Blood Loss in Abdominal Surgery.*

OPERATION	NO. OF CASES	BLOOD LOSS	RED-CELL LOSS	PLASMA LOSS
		cc.	cc.	cc.
Gall-bladder procedure	6	690	270	420
Large-bowel procedure	4	1630	460	1190
Gastric resection	11	1870	440	1490

Figure 9 shows the changes produced as a function of time. Dextran, gelatin and serum albumin are approximately equally effective in expanding the blood volume and have a more lasting effect than plasma.[67] Saline controls showed no significant change in the blood volume fifteen minutes after completion of a 500-cc. saline infusion.

Summary and Conclusions

The labeled-red-cell technic for blood-volume measurement is simple and is applicable to routine determination of the blood volume in a general hospital. The equipment required may be found in any clinical laboratory except for the Geiger-Müller counter and scaler. The counter and scaler used in this study is of the simplest inexpensive type and may be handled with little difficulty. Several

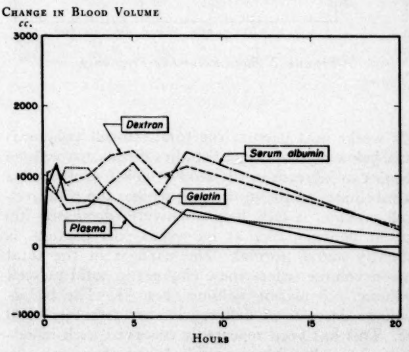

FIGURE 9. *Blood-Volume Increase Produced by Dextran, Gelatin, Serum Albumin and Plasma.*

technicians have been readily trained in the technics for the labeling of the cells, the measurement of P^{32} and the calculation of the blood volume. This test requires only a physician for supervisory management and for the injection of the labeled cells.

The results of approximately 1500 determinations of the blood volume done in our laboratories on patients with various diseases are presented, and the superiority of the measurement of blood volume over the red-cell count and hematocrit is pointed out. The determination of the blood volume should find wider usefulness in the handling of medical and surgical problems, in which the value of the oxygen-carrying power and the plasma constituents of total blood volume are important factors.

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MEDICAL INTELLIGENCE

THE CULDOSCOPE AS AN AID TO DIAGNOSIS IN EARLY VIABLE ECTOPIC PREGNANCY*

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NEW YORK CITY

A REVIEW of patients with ectopic pregnancies operated on at Harlem Hospital in the last ten years shows a marked rise in the incidence each year. In 1942 there were 26 such cases, and that number increased annually until in 1950 there were 88 cases in which the diagnosis was verified at laparotomy. It is possible that this increase in the number of ectopic pregnancies can be ascribed to the advent of antibiotics. It is postulated that with these new drugs a salpingitis can be corrected before complete closure of the tube — but not before some tubal damage, such as adhesions, tortuosity or pseudofollicular salpingitis — has taken place. Because the ostium and lumen of the tube have not been completely closed, fertilization is still possible, but in the course of the journey down the tube to the endometrial cavity the newly fertilized ovum is beset with many pitfalls that may hinder its trip to safety and cause it to develop within the tube itself.

This presentation is not designed to discuss the pathogenesis of ectopic pregnancy, or to comment on the statistical analysis, but to report a case that is different from the usual ectopic pregnancies that are seen on a large gynecologic service. The case described below demonstrates that occasionally the patient with the unusual type of ectopic gestation can be followed in the hospital, watched carefully for danger signs and then operated on when the diagnosis has been established well beyond the point of conjecture.

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CASE REPORT

Mrs. R. W. (H. H. 51-20913) was admitted to the hospital on December 4, 1951, with a complaint of pain and spotting for 10 days, and in no acute distress. She stated that her last menstrual period had begun on October 1, lasting 3 days, and that her previous period had begun on September 2, lasting 3 days. She started to spot 10 days before admission, and at the same time a persistent crampy pain developed in the left lower quadrant. The pain was nagging; at no time was there an overwhelming attack or a disabling episode. There was no fainting and no referred shoulder pain, but the patient complained of being dizzy on several occasions since the onset of her present illness.

The menses had begun at the age of 13, and were regular in cycles of 28 to 30 days, lasting 3 days, with dysmenorrhea on the 1st day. There were no irregularities noted.

The patient had had 3 normal full-term deliveries, the last of which had occurred 6 years previously. There was no history of abortions.

For the past year she had been treated with antibiotics in the Outpatient Department for "inflammation," but a specific history of venereal disease was denied.

Physical examination showed a well developed, well nourished Negress in no acute distress. Examination was negative except for the abdominal and pelvic findings. The abdomen was tender to palpation in all areas, with rebound tenderness in the left lower quadrant. No fluid wave was elicited; there was no dullness to percussion, and no masses were felt. The external genitalia were normal, the introitus was parous, and the mucosa of the vagina was normal in appearance. The cervix was anterior, with a moderate amount of tenderness on motion, and minimal softening of the external os. The fundus, which was anterior, was of a size compatible with a pregnancy of 6 weeks, and was tender to palpation and motion. In the left fornix was a 6-cm. indurated, tender cystic mass closely adherent to the body of the uterus. The right fornix was without demonstrable disease. Speculum examination revealed moderate cervical erosion, no bleeding and a small piece of tissue protruding from the cervical os. This was removed and sent to the pathology laboratory for microscopical examination.

The temperature was 98.6°F., and the pulse 86. The blood pressure was 116/70.

Examination of the blood disclosed a red-cell count of 4,340,000, with a hemoglobin of 10.4 gm., and a white-cell count of 7000. The sedimentation rate was within normal limits. Examination of the urine was negative.

A diagnosis of ectopic pregnancy, probably in the left tube, with abortion, was made on the basis of amenorrhea, pain, spotting, presence of a mass, normal temperature and normal sedimentation rate. However, intrauterine pregnancy with disease of the adnexa could not be ruled out, and because of the patient's obviously good condition and the lack of any free fluid in the abdomen, it was decided that she should be watched carefully and further laboratory studies done. Daily determinations of hemoglobin, sedimentation rate, blood pressure and temperatures varied only slightly. There was never a drop in the hemoglobin below 10.0 gm., and the sedimentation rate remained normal; the temperature showed no rise, and the blood pressure remained within 10 points of the initial reading. An Aschheim-Zondek test 2 days after admission was reported as positive. The pathology report of the tissue found in the cervix on admission was "decidual reaction of the endometrium." Another piece of tissue passed subsequently was called "blood clot."

As a further aid to diagnosis culdoscopy under saddle-block anesthesia was performed 10 days after admission, and the suspected condition was demonstrated (Fig. 1). The

uterus was injected and slightly enlarged. The sigmoid was visualized in the left lateral gutter. The left tube was grossly enlarged, dilated, tortuous, sac-like and closely adherent to the left side of the uterus. On the serosal surface of the tube were tags of yellow fibrinous material. The fimbriated end of the tube was not seen. The contents of the tube visualized against the reflected light of the culdoscope appeared bluish. The left ovary was enlarged and contained one yellow cyst at its lower pole. The right tube revealed minimal nodular salpingitis, and the right ovary was normal in size and shape. The diagnosis made from the culdoscopic findings was ectopic pregnancy (left tube), probably tubal abortion in type, presenting some old blood on the tubal surface, indicating that leakage had taken place some time before.

Upon re-examination 1 day later the left-sided mass appeared to be larger than before, and laparotomy was decided upon. A second Aschheim-Zondek test before operation was positive. At operation the uterus was found to be enlarged to a size consistent with a pregnancy of 6 to 8 weeks, and the

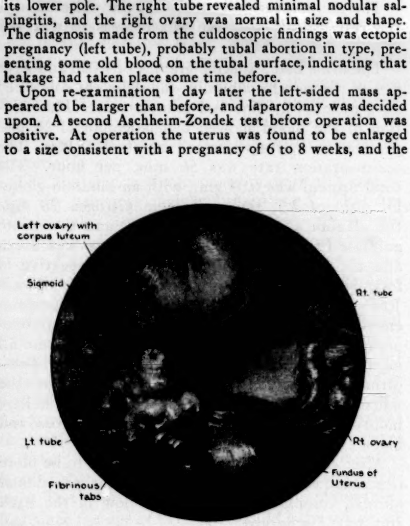

FIGURE 1. *View of the Pelvic Lesion as Seen through the Culdoscope.*

The left hematosalpinx is clearly visualized, with the fibrinous elements on the serosal surface and the entire mass adherent to the posterior surface of the uterine fundus.

right adnexa were normal except for minimal nodular salpingitis. On the left was a large hematosalpinx, 9 by 5 cm., irregular, with tags of yellow-brown fibrinous material on the serosal surface. The fimbriated end was closed. The ovary was only slightly enlarged and contained a yellow cyst at its lower pole. There was no free blood in the peritoneal cavity. A left salpingo-oöphorectomy was done, and the abdomen closed in layers. The patient's course was uneventful, and she was discharged from the hospital on the 10th postoperative day.

The specimen was opened with great care and revealed the products of conception in a fresh state. The fetus with eye and limb buds could be clearly seen surrounded by placental tissue. At the point where the fibrinous material was found on the serosal surface of the tube was a break in the continuity of the tubal musculature and serosa indicating that this was the site of a previous break-through. The microscopical diagnosis was "fallopian tube containing products of conception and ovary containing a corpus luteum of pregnancy."

DISCUSSION

Because of the peculiarity of this particular case of ectopic gestation, the patient was followed with daily laboratory data, hormone tests and culdoscopy, to determine the exact anatomic nature of the condition, which proved to be a tubal pregnancy with a previous rupture at one point, although not through a large vessel; probably, a small amount of blood had spilled into the peritoneal cavity, the rent in the tube sealing over, and the viable fetus had distended the tube and produced vague abdominal signs and symptoms. The resulting hematosalpinx was preparing itself for rupture and massive hemorrhage, and the patient then, in all probability, would have arrived at the hospital in the usual bled-out state of a rupture with ectopic pregnancy, requiring rapid emergency surgery and blood replacement. The sequence of events in this case afforded the unique opportunity to follow a slowly fulminating ectopic pregnancy with clinical and visual (culdoscopic) aids.

I am indebted to Dr. M. Leo Bobrow, director of the Gynecological Service of Harlem Hospital, for his help in this presentation and for his permission to publish the case, and to Mr. Alfred Feinberg for his preparation of the culdoscopic drawing.

MEDICAL STUDENTS

AN impression exists that the number in attendance at medical schools is considerably smaller, in the aggregate, the present season, than usual. This is gratifying intelligence; but without a footing up of the catalogues, it is quite impossible to determine the point. Too many have been entering the profession for the last ten years. If government would commission ten where one is now taken into the public service, it would present a prospect of encouragement: but we have no great standing armies requiring a numerous staff of surgeons; the navy is economically provided with them, and merchant ships rarely venture upon the expense of a medical officer. There is so little to look forward to, in regard to income from business, in the present crowded state of the profession throughout the whole length and breadth of the land, that no one can be surprised should there be a falling off of candidates at the schools. At the West, there is much more room for an increase in the medical ranks than in New England. There a physician may grow up with a town, and hold that position which is due to enterprise and talent; but in the old Atlantic States, in which every order and kind of medical adventurers abound, a young Æsculapian finds himself in a limited sphere of action, with no immediate encouragement, and discovering that life is too precious to be frittered away in hopeless expectancy, very many abandon the field in disgust, and turn their attention to something else.

From "Medical Intelligence."

Boston M. & S. J., December 22, 1852.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 38441

PRESENTATION OF CASE

A fifty-two-year-old man was admitted to the hospital because of epigastric pain.

Four days prior to entry severe constant, throbbing midepigastric pain, which was distributed in a band around the entire abdomen just below the umbilicus, suddenly occurred a few hours after the evening meal. The pain was severe for about ten minutes and then subsided to a steady, nonincapacitating ache, which seemed to go straight through to the back. The pain was slightly throbbing but not crampy. The patient had a slight urge to vomit, but when he induced vomiting manually, there was no relief of the pain, which persisted without any noticeable change until admission; it was not affected by movement or coughing. The temperature was allegedly 100.6°F., and he had had some malaise, but no chills. He had taken an enema daily from the day of onset without any significant results until the day of admission, when he had a good result, with some decrease in pressure in the lower abdomen, but no relief of the steady pain. Prior to the onset of pain his bowel movements had been regular, and his appetite good. There was no history of similar attacks, hematemesis, vomiting, food intolerance, urinary symptoms, dyspnea, orthopnea, jaundice, leg pains or loss of weight.

He had had periodic pain in the lower back for forty years. Four years before admission during exercise he had experienced a sudden acute low-back pain for which he remained in bed for a week; the pain gradually subsided but recurred occasionally in a less severe form after exercise; the character of the pain and its location were different from those of the present attack.

Physical examination revealed an alert, well developed, pale man in no acute distress. The heart and lungs were normal. The abdomen was soft and not distended; there was some tenderness upon deep palpation of the midepigastrium. No spasm or masses were felt. There was no costovertebral-angle tenderness. Peristalsis was normal. Rectal examination was negative. There was full movement of the spine, with no pain and no local tenderness. Movement and reflexes in the legs were normal.

The temperature was 101.6°F., the pulse 82, and the respirations 20. The blood pressure was 160 systolic, 100 diastolic.

The urine had a specific gravity of 1.020 and gave a ++ reaction for albumin; the sediment contained an occasional hyaline and granular cast. Examination of the blood showed a hemoglobin of 16 gm. per 100 cc. and a white-cell count of 13,000. The sedimentation rate was 56 mm. per hour. The total protein was 6.04 gm., with an albumin-globulin ratio of 2.3, the nonprotein nitrogen 28 mg., the alkaline phosphatase 5.2 units, and the serum amylase 19 units per 100 cc.; the lipase was 5 cc., and the cephalin-flocculation test was negative in forty-eight hours. The urine was negative for Bence-Jones protein. A gastrointestinal series, barium-enema examination, Graham test and roentgenogram of the lower dorsal and lumbar spine were all negative. Sigmoidoscopic examination showed hemorrhagic spots, 2 to 3 mm. in diameter, on the mucosa of the rectum but no other abnormality; biopsy of these showed normal rectal mucosa and blood clot.

After eight days the patient appeared to be more comfortable; he had a temperature that was almost normal, complained only of pain low in the back and was discharged.

Two weeks after discharge he was still complaining of generalized weakness and of specific weakness of his legs; his physician noted a hemoglobin of 55 per cent and a white-cell count of 12,400 and started him on iron and Vitamin B_{12} therapy. Six weeks after discharge abdominal pain recurred at some time during the night and apparently grew more severe. His physician, who was called at 8:00 a.m., found him pale, unresponsive, pulseless and gasping for breath; he died a few minutes later.

DIFFERENTIAL DIAGNOSIS

DR. EARLE M. CHAPMAN*: One of the most important things to me is what this man's occupation was and what the exercise was that precipitated the pain.

DR. BENJAMIN CASTLEMAN: He was employed in the boiler room of a soap factory as a foreman.

DR. CHAPMAN: What did he do as a foreman? Did he have to lift barrels?

DR. CASTLEMAN: I doubt if a foreman lifts anything.

DR. CHAPMAN: Some do very heavy work.

It is evident that this man, who was fifty-two years old and may have aged rapidly, had widespread vascular disease and hypertension, which I

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think had affected his kidneys — a certain amount of nephrosclerosis or arteriolar Bright's disease; then suddenly something happened to him. What happened? I think it was a vascular accident. The question then arises, Where did the vascular accident occur? I think it was either in the mesentery or in the abdominal aorta. Thrombosis of the mesenteric artery might produce the symptoms suggesting disease in the digestive tract, which all the studies seemed to rule out (including acute pancreatitis), without producing any recognizable changes in the digestive tract. I think it is more likely that the mischief occurred in the abdominal aorta. There may have been a weakness of the aortic wall, with dissection.

The first clue in the reconstruction of this case is that the pain was slightly "throbbing." That fits with vascular disease. Then, there was a thrombosis or a dissection of the aorta to change the continuity of blood flow at the level of the renal artery, thus affecting the kidneys at the same time, or perhaps it was slightly below the level of the kidneys. Anatomically, I think I am hard put to it; if the pain was midepigastric and high up, the thrombosis or dissection may have included the renal artery, but if the pain was below the umbilicus, the vascular disease may have been below the renal arteries. An interesting point in the subsequent history was the weakness of the legs without changes in reflexes or other findings that would suggest to me interference with the blood supply to the vessels of the legs. To tie in the aching back that the patient had had since the age of twelve, I should have to assume that there was some type of congenital anatomic defect. I am going to stick my neck out and say that this was a dissection of the aorta, perhaps with thrombosis, and that the final episode was further dissection, with extravasation of blood through the previously dissected area.

Among the other things to consider is an accident that occurred within the spinal canal. No lumbar puncture was done. Evidently, the clinicians who first saw the patient did not suspect that pain of that nature might be arising in the central nervous system or the spinal cord; the reflexes were normal. The suddenness of the death in association with blood loss raises the possibility of a bleeding lesion in the gastrointestinal tract that had been missed in the x-ray studies done in this hospital six weeks before entry. I do not suspect an ulcerating lesion in the digestive tract because I believe that he had a penetrating lesion in the aorta that began six weeks before entry and that death occurred as a result of rupture with internal hemorrhage.

I had hoped to find something in his occupation that had contributed to his illness; he was a workman, he labored hard, he strained, he lifted things perhaps.

Dr. Castleman: The first attack of pain came on while the patient was sitting still watching television.

Dr. Alfred Kranes: Do you think the first intimal tear occurred when the first pain occurred? Did it start in the thoracic aorta with epigastric pain?

Dr. Chapman: And then it worked downward from the thoracic to the abdominal aorta? The pain was defined as being band-like, below the umbilicus, though it was first called epigastric; I do not see how I can say.

Dr. Castleman: Dr. Marks, you took care of this patient; have you any comment?

Dr. H. E. Marks: The patient had a history of stomach trouble for about ten years that he said occurred in episodes about once a month. At the time of the onset of pain that brought him to the hospital, he had had an extraordinarily large evening meal and several snacks, including one or two bananas, after supper. After the last snack — a banana — he was seized with epigastric pain that doubled him up, and he took to his bed. In the morning when I was called to see him, the pain had become less acute, but he did have some rigidity of the abdominal musculature — not boardlike. I thought there might well have been a minute peptic perforation that tended to seal itself. The white-cell count was 20,700, so he was given terramycin followed by aureomycin and later dihydrostreptomycin; the white-cell count dropped a little. On the third day he was referred to the hospital, and though he felt much better the white-cell count was still high.

The night before his death — I had known this man for ten to fifteen years — he was walking and visiting. He again had pain in the abdomen, lay down for an hour and then returned home. The pain regressed during the night, but at 7:30 the next morning his wife called me and said that she thought he had an attack of appendicitis — he had pain in the right side down in the lower abdomen. She asked me to see him that morning. Before I got out the door, the telephone rang again and his wife asked me to hurry. When I saw him, his eyes were rolled upward, and his lips were quite white; it was obvious that he was bloodless; there was no blood outside the body, and there was only one place it could be and that was in the abdomen.

Dr. Kranes: Was the patient hypertensive before those episodes occurred?

Dr. Marks: His blood pressure varied from 115 to 140 systolic.

Dr. Chapman: I have enjoyed hearing Dr. Marks' history of his patient. The history of stomach trouble for about ten years raises the question of an ulcer through which at the end the patient may have been losing large amounts of blood. Dr. Marks, did you ever have x-ray studies of his digestive tract?

DR. MARKS: No, I do not recall having any x-ray films taken.

CLINICAL DIAGNOSIS

?Duodenal ulcer.

DR. CHAPMAN'S DIAGNOSIS

Ruptured dissecting aneurysm of abdominal aorta.

ANATOMICAL DIAGNOSES

Ruptured dissecting aneurysm of descending thoracic and abdominal aorta, old and recent.

Retroperitoneal hemorrhage, with rupture into peritoneal cavity.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: It was through Dr. Marks, the patient's family physician, that we obtained permission for autopsy.

At autopsy the abdominal cavity contained about 2 liters of blood, 1 liter of which was clotted. The blood clot that remained in the right pelvis after the 2 liters of blood had been removed from the abdominal cavity was fairly low in the retroperitoneum. When the descending colon was pushed to one side, we could see a large mass of blood in the external coat and serosa of the large bowel that appeared to be a retroperitoneal extension from the large pelvic hematoma. Pressure on the bowel pushed blood into the peritoneal cavity through a perforation. We believe that all this blood originated retroperitoneally in the pelvis, extended up into the abdomen and ruptured into the peritoneal cavity near the descending colon. When that blood was washed away, we found a dissection of the aorta; the intimal tear from which the dissection extended downward appeared recent and was in the descending thoracic portion just beyond the orifice of the left subclavian artery. Part of the blood in the dissecting channel was old and organized; part was fresh.

I assume that seven and a half weeks before death a dissection occurred without an intimal tear within the media, with later organization of the hemorrhage; that just before death another dissection occurred as the result of the recent intimal tear with fresh blood dissecting downward; and that an external rupture in the region of the right iliac artery was the final episode. Not all dissecting aneurysms arise from an intimal tear. It has been shown that the primary disease is in the media and that the hemorrhage may be present in the wall of the aorta without an intimal tear. We did find in the media degeneration of the mucoid type that we see associated with medionecrosis cystica such as Erdheim has described. The right iliac artery showed evidence of dissection, which probably cut down the blood supply to the legs terminally. The right kidney was slightly sclerotic but was otherwise normal.

DR. ARTHUR S. PIER, JR.: Is this not unusual in an aorta without hypertension?

DR. CASTLEMAN: Yes; most of the patients have hypertension. This patient's heart was small; there was no hypertrophy to suggest hypertension.

DR. JOHN T. QUINBY: Were there occlusions to the renal arteries?

DR. CASTLEMAN: There was no dissection of the renal arteries. There was some dissection of the mouths of the superior mesenteric artery and the celiac axis; the patient did not live long enough for any anatomic changes to be produced in the abdominal viscera.

FIGURE 1. *Anteroposterior Bucky Film. Thickening of perispinal soft tissue is indicated by the arrows.*

DR. STANLEY M. WYMAN: I think there is evidence of extravasation of blood on the films of the thoracic spine (Fig. 1).

DR. CASTLEMAN: The medial hematoma was certainly large enough for one to expect that it could have been seen in the x-ray films of the aorta.

DR. CHAPMAN: Dr. Kranes pointed out that I did not ask to see the x-ray films; I am sorry I did not ask to see them.

DR. WYMAN: You did not need them. This shadow along the spine is present on two films of the stomach; in the lateral view there is some clouding of the posterior costophrenic angle.

DR. CHAPMAN: If you saw a similar picture, would you be willing to say that it looked like a dissection?

DR. WYMAN: We see this most commonly with lymphoma or other retroperitoneal tumors, but we have seen it with hemorrhage from a spleen and with other types of retroperitoneal hemorrhage.

DR. CASTLEMAN: It was not retroperitoneal hemorrhage in a strict sense; it was in the wall of the aorta.

DR. WYMAN: It produces the same effect radiologically as a retroperitoneal hemorrhage does.

CASE 38442

PRESENTATION OF CASE

A fifty-one-year-old Negress was admitted to the hospital because of abdominal pain.

The patient stated that she had been well until two weeks before entry, when she noted the sudden onset of severe crampy mid-abdominal pain that radiated to the right upper quadrant and back. She was nauseated but did not vomit. During the next few days the pains recurred intermittently, and because of this the patient did not go to work. She became somewhat anorexic and felt generally fatigued. Several days later she noted that the urine was dark red. She did not observe the color of her stools. During the following week the attacks of right-upper-quadrant pain continued but were not as severe as the initial one. There was no definite relation of pain to meals; however, she stated her appetite had been poor after the onset of the pain. She felt "bloated." About a week before admission she noted "blood-shot" eyes, and for the past few days the abdomen and forearms had itched. She had not had any chills and had not felt feverish.

The past history was noncontributory except for "indigestion" for about one year. Because this was aggravated by fried or fatty foods, the patient had avoided them.

Physical examination showed an obese woman in no acute distress. The scleras were questionably jaundiced. The right lobe of the thyroid gland was enlarged. The heart and lungs were normal. There was an epigastric hernia. Tenderness without spasm was present over the right upper quadrant, and there was an ill defined mass located well laterally beyond the edge of the rectus muscle that was not very tender. There was no costovertebral-angle tenderness.

The temperature was 100°F., the pulse 60, and the respirations 20. The blood pressure was 200 systolic, 100 diastolic.

The urine was dark amber, had a specific gravity of 1.018, gave a ++ reaction for albumin and a ++++ reaction for bile and contained urobilinogen only in a 1:2 dilution. The blood hemoglobin was 14 gm.; the white-cell count was 5000, with 71 per cent neutrophils, 15 per cent lymphocytes, 9 per cent monocytes, 4 per cent basophils and 1 per cent eosinophils. The serum protein was 7.9 gm., the albumin 4.03 gm., the globulin 3.16 gm., the nonprotein nitrogen 33 mg., the alkaline phosphatase 13.2 units, the serum bilirubin 7.7 mg. direct and 9.8 mg. total per 100 cc. The prothrombin time was 14 seconds (normal, 13 seconds), the thymol turbidity 2.0 units per 100 cc., and the cephalin flocculation negative in twenty-four hours and + in forty-eight hours. A stool specimen was clay colored and guaiac negative. A roentgenogram of the chest showed a soft-tissue mass in the right lower part of the neck and superior mediastinum, with diffuse narrowing of the trachea just above the clavicle. There were linear shadows in the right-lower-lung field near the diaphragm consistent with platelike atelectasis. On the left was a similar density lying close to the left border of the heart. The heart shadow was moderately enlarged, chiefly in the region of the left ventricle, with a cardiothoracic ratio of 15:26 cm. The aorta was quite tortuous and probably calcified. A plain film of the abdomen was normal. A Graham test showed no concentration of the dye in the gall bladder.

In the hospital there was little change in the patient's condition. On the seventh hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. DANIEL S. ELLIS*: May I see the x-ray films?

DR. JOSEPH HANELIN: The chest films show concentric narrowing of the trachea in the lower portions of the neck and a soft-tissue density at this level on the right side, compatible with an enlarged thyroid gland. The heart is enlarged to a fair degree, predominantly the left ventricle. There are linear streaks at either base that appear to be due to atelectasis. There is no evidence of congestive change in the lungs. The abdominal film is normal. There is scattered gas in the bowel without abnormal distention. I can see no definitely abnormal masses in this film. Cholecystograms show no disease in the gall bladder. There is just vaguely made out a round density in relation to the lateral edge of the liver on the right that may represent a portion of the mass that was felt clinically. I see no opaque stones. There are calcified lymph nodes in the right lower portion of the abdomen.

DR. ELLIS: There is an area of increased density with what appears to be a soft-tissue mass. No gallstones?

DR. HANELIN: There is superimposition of soft-tissue structures, but I do not believe there is evidence of an opaque stone.

DR. ELLIS: You can see no gallstone ileus?

DR. HANELIN: No.

DR. ELLIS: This patient's major problem seems to have been obstructive jaundice. She had hypertension; I assume that the renal findings were

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secondary to hypertension and arteriosclerotic renal disease. In reading over the protocol I suspected that the right-upper-quadrant pain might have been of renal origin but I do not note any further evidence to support that impression. This vague ill defined mass to the right of the right-rectus muscles could have been gall bladder, kidney, or tongue of the liver. From these x-ray films it does seem that the liver went down very far. The mass is said to have been tender. This mass could have been the gall bladder. It would be unusual for a large palpable gall bladder to be tender if due to obstruction without infection. In the absence of a neoplasm obstructing the common duct, a large palpable gall bladder may result from an empyema but then it is usually tender and is associated with an elevated white-cell count.

DR. MELVIN J. GLIMCHER: On admission to the Emergency Ward, she did have tenderness with slight spasm in the right upper quadrant. In addition the liver edge was felt about 3 or 4 finger-breadths below the costal margin and was tender. One could follow the edge of the liver medially; just lateral to the edge of the rectus muscle was a large, tender, globular mass. The spasm and tenderness gradually subsided in a few days.

DR. ELLIS: Was the mass unattached to the liver?

DR. GLIMCHER: Yes.

DR. ELLIS: Did it descend with respiration?

DR. GLIMCHER: Yes.

DR. JOHN W. RAKER: I think it is fair to say that our impression was that this mass was the gall bladder.

DR. GLIMCHER: I suppose the reason the mass was termed ill defined in the protocol is that only half the physicians who examined the patient could palpate it. To those of us who did feel it, it was anything but ill defined.

DR. ELLIS: We have recently had such a case in which half the physicians palpated a mass. The half that palpated it had no uncertainty that they felt it and believed it was the gall bladder. If one feels something and has no doubt about it, one has felt it, and that is that.

I think the patient had obstructive jaundice. There is nothing in the protocol to suggest parenchymal liver disease. There were a normal cephalin-flocculation test, a normal albumin-globulin ratio, clay-colored stools, decreased urinary urobilinogen, an elevated alkaline phosphatase and jaundice; all this adds up to obstructive jaundice. She should have been operated on.

The question is, What did the surgeons find at operation? As always, one does not know what is in a box until one opens it. Judging from the protocol, I should have operated on this patient with a diagnosis of chronic cholecystitis and cholelithiasis. Since she had midabdominal, cramp-like pain, I should have wondered whether she had passed a gallstone through the gall bladder into the small intestine. Yet I should have expected her to have more reaction to that, and I certainly could not have made that diagnosis preoperatively. The other possibilities are carcinoma of the gall bladder, common duct or head of the pancreas, the last being most likely. Again, there is nothing in the protocol to suggest a neoplasm except that she had symptoms for a year; she had no weight loss, no anemia and nothing on physical examination to make me suspect that there was a neoplasm. In a fifty-seven-year-old woman with this story of pain and these physical findings the presumptive diagnosis should be gall-bladder disease — chronic cholecystitis and gallstones.

Did she have a cyst of the liver? That diagnosis is rarely made preoperatively. She did not come from the Mediterranean area, where echinococcus cyst is common. Cyst of the liver is a possibility, but I can do no more than mention it.

The pain is consistent with a lesion in the hepatic flexure of the colon. She did not have a barium-enema examination, and nothing in the history suggested a lesion in the hepatic flexure.

I shall make a diagnosis, simple as it may seem, of cholecystitis and cholelithiasis. There are other possibilities, which I have mentioned.

A PHYSICIAN: What did you consider the mass in the neck was?

DR. ELLIS: That was the thyroid gland as far as I can determine and played no part in the obstructive jaundice. I do not believe she had a thyroid carcinoma with metastases involving only the biliary tract.

DR. JACOB LERMAN: Do you think there was a common-duct stone?

DR. ELLIS: There must have been. She might have had a ball-valve stone that blocked the duct at the times when the gall bladder could be palpated. I assume that she had a common-duct stone as well as the stone that Dr. Hanelin showed me!

A PHYSICIAN: Was a blood amylase determination done?

DR. ELLIS: There is no mention of it in the protocol. The pain is suggestive of pancreatitis, but, again, one cannot be sure of that before operation.

A PHYSICIAN: Did you consider carcinoma of the pancreas?

DR. ELLIS: One has to. The patient had a palpable gall bladder and jaundice. Her lack of weight loss and relatively acute onset of symptoms other than the indigestion made me believe it probably was not pancreatic carcinoma.

DR. ALLEN G. BRAILEY: Would you consider the ampulla of Vater a likely place for a carcinoma?

DR. ELLIS: The stools were guaiac negative. If carcinoma was present, I should think it was more likely to be in the pancreas than in the ampulla.

DR. BENJAMIN CASTLEMAN: Dr. F. B. Hershey operated on this patient, but is not here. Could you tell us about the operation, Dr. Raker?

DR. RAKER: On the service we reasoned much as Dr. Ellis did. We were impressed by two things: the first was that the patient seemed to have severe steady abdominal pain at the time of admission and several other episodes during the entire preoperative period in the hospital, and the other was the mass. A number of us were impressed by the presence of a mass that we thought was tender and probably represented an acutely obstructed gall bladder.

CLINICAL DIAGNOSIS

Common-duct stone.

DR. ELLIS' DIAGNOSIS

Chronic cholecystitis and cholelithiasis.

ANATOMICAL DIAGNOSIS

Adenocarcinoma of head of pancreas.

PATHOLOGICAL DISCUSSION

DR. RAKER: We operated on the patient with a diagnosis of obstructive jaundice, believing that she had a common-duct stone rather than a malignant lesion and were somewhat surprised to find a large carcinoma of the pancreas obstructing the common duct. She had a palliative operation only.

DR. CASTLEMAN: I was just wondering why a barium meal was not given; from the surgical description there was puckering of the duodenum, and perhaps the films of the barium swallow would have suggested the diagnosis.

DR. ELLIS: A barium meal is a most important diagnostic measure and should be done in such cases before operation.

DR. RAKER: Postoperatively, she did have a barium swallow, which showed no major change in the duodenum.

DR. CASTLEMAN: Was the gall bladder enlarged?

DR. RAKER: It was enlarged and tense, and it showed a thinned wall. It was not acutely inflamed.

DR. HANELIN: The postoperative films show the anastomosis of the gall bladder to the stomach.

DR. ELLIS: Can you see the duodenal loop?

DR. HANELIN: I think this is the loop, and it appears widened.

DR. CASTLEMAN: The microscopical sections confirmed the diagnosis of adenocarcinoma of the pancreas, and biopsy of the liver showed severe bile stasis, without evidence of cirrhosis. Are you planning to do anything more for this patient?

DR. RAKER: She has had all the surgery that will be done — namely, a cholecystogastrostomy and a posterior gastroenterostomy.

A PHYSICIAN: What was in the chest?

DR. RAKER: There was a palpable multinodular goiter that had nothing to do with the rest of the problem.

DR. ELLIS: The moral of this lesson is that one will be right more often and wrong very seldom if he believes in and allows himself to be guided by Courvoisier's law when confronted with such a problem.

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THE PERMANENTE PLAN'S FIRST TEN YEARS

WITH the cost of medical care rising progressively, with insurance plans such as Blue Cross and Blue Shield forced to increase their premiums while their benefits provide for decreasing proportions of the faster rising costs, and with less and less of the worker's income from wages or salaries available for savings, it is a question whether the supplying to considerable segments of the people of some form of prepayment plan for total medical care can be indefinitely postponed. It is therefore incumbent on the medical profession, as well as other interested parties, to continue to study carefully every apparently successful experiment designed to provide complete medical care of the highest quality to large groups of people at a cost that they can afford and that they can budget. One experiment deserving such scrutiny is the Permanente Plan.

In the Tenth Anniversary Issue of the *Permanente Foundation Medical Bulletin*,* issued in August, 1952, Dr. Sidney R. Garfield traces the development and growth of the Permanente Plan in the Pacific Coast states. It was originally designed to meet the serious dearth of facilities and medical services in the San Francisco Bay area created by the mass dislocation of people into wartime shipbuilding. Actually, it evolved as the result of a decade of earlier attempts by a group of interested and far-seeing persons to provide the best hospital and medical care to average workers at a cost that they could afford. According to its director, the plan, as it actually worked out, was the outstanding wartime medical service outside the armed forces; the list of its achievements seems to bear out that estimate.

At the end of the war in 1945, when shipbuilding was discontinued and the workers were dispersed throughout the country, the relatively few who remained served as a nucleus for the continuation of the plan on a community basis. Now, in 1952, the Permanente Plan serves 250,000 members in California, Oregon and Washington, as well as large numbers of patients who are not members. The acceptability of the plan and its popularity are fully attested by the fact that new facilities are now under construction that will provide for an increase in membership to 400,000.

The scheme was designed to eliminate the waste resulting from poorly planned facilities and from the ineffectual co-ordination both among the physicians themselves and between them and the institutions in which they worked. It was accomplished by a well co-ordinated group practice operating in well planned medical centers. It is a prepayment plan based on the insurance principle for the provision of a comprehensive medical service. The fee for service was abolished, but all the prepaid funds have been going to physicians and hospitals. It has there-

*Garfield, S. R. Report on Permanente's first ten years. *Permanente Found. M. Bull.* 6:1-12, 1952.

fore provided the greatest incentive and laid the foundation for the genuine practice of preventive medicine by making the healthy person an asset and the sick person a liability.

Details of the plan are worthy of study, for, although Dr. Garfield's presentation might be interpreted as being tinged with enthusiasm and self-interest, the facts of its accomplishment are impressive. It has also been a financial success. In the ten years since the plan was established and while it was developing, participating physicians and professional personnel have been paid $23,500,000, and over $10,000,000 has been paid to nonprofessional personnel and $1,500,000 to outside physicians and professional people.

The organization consists of the following parts: a foundation that is a charitable trust providing facilities and funds for teaching, training, research and charity; a health plan that enrolls members, collects funds and apportions them among the hospitals, medical groups and administration; hospitals that are nonprofit corporations operating medical centers; and medical groups of independent physicians organized in partnerships, each covering a regional service area. The incomes of the doctors in these groups compare favorably with those of physicians in private practice in the same area.

In closing his report Dr. Garfield makes the following statement of the future and of the aspirations of the Permanente Plan:

> We are striving to prove (1) that high quality medical care and hospital service can be rendered to the people at a cost which they can afford; (2) that this can be done to the benefit of all parties concerned — the people, the physicians, the hospitals; (3) last and not least, to prove that all this can be done by *private enterprise* without necessity for government intervention. . . .
>
> . . .The great interest displayed by doctors, labor, government and the people in the "Permanente idea" encourages us to believe that the accolade of "mission accomplished" cannot be too far off. The workers at Permanente feel that new horizons are opening up for the coming decade. . . .
>
> . . .The lifting of barriers to the financing of facilities, as demonstrated by the projected new construction, cannot help but make an impressive demonstration to the physicians and hospitals of the country. The excellence of these new facilities, their innovations, the quality of work being performed, the educational and research programs developed will add in no small measure to pyramiding evidence of worth and soundness.

Certainly, this plan is worthy of careful study by physicians throughout the country as one type of program that may not only erect further defenses against the encroachment of socialized medicine but actually provide more and better medical service, at lower cost, and at the same time maintain the dignity of both doctor and patient.

SPIRIT INCORRUPTIBLE

THE London *Lancet* has recently concluded the publication of a long series of short essays on "disabilities" — personal accounts written by and drawn from the experience of lay persons who had adjusted themselves with surprising success to various physical handicaps with which they had been afflicted. Many of the articles were refreshing in that they were written with an ingenuousness resulting from a lack of any precise knowledge of disease and with an absence of restraint that could be given only by anonymous publication. These were communications in which anonymity was of value.

Of similar design yet quite different in their execution are the more sophisticated articles comprising the volume *When Doctors Are Patients*, a collection that was started by the late Dr. Max Pinner and carried to its conclusion by Dr. Benjamin F. Miller.* Its thirty-three descriptions of the authors' reactions to their diseases are documentary accounts, written by experts, all but eight of whom have been willing to allow their testimony to appear over their names. The subjects are varied, — for physicians are vulnerable to the same corruptions of the flesh with which the rest of mankind is visited, — ranging from the comparatively benign disability of convalescence from an acute illness to cancer of both breasts; from sinusitis to morphine addiction; and from weather sensitiveness to heart disease in its various forms, which seems to be the final illness of so many physicians, among others.

When Doctors Are Patients is strong in its flavor of authenticity because of the quality of its authorship, and yet in some ways this authenticity is almost its undoing. For in the effort to reveal to an impersonal public their private and personal ordeals the contributors have exposed themselves almost too much; the attempt to avoid restraint has sometimes resulted in constraint. There is

*Pinner, M., and Miller, B. F. *When Doctors Are Patients*. 364 pp. New York: W. W. Norton and Company, Inc., 1952.

self-consciousness in standing naked before a mirror to draw a portrait of oneself.

The book is nevertheless a dignified and on the whole a successful setting down in black and white of the accounts of productive introspection. Many lay readers, similarly afflicted, will find comfort or inspiration in its pages; many physicians with the same problems will learn, if not to heal themselves, at least how other physicians have faced up to these problems.

Possibly the clearest exposition of one's reaction to degenerative disease is found in the closing sentences of Abraham Myerson's deposition, penned but a few months before his death in 1948:

> In the bright sunshine of today, writing at my desk, I feel reasonably well, and though I would not bet that I shall live six months, it *seems* as if the real *I* is indestructible. I think psychiatrists preach nonsense when they say: "adjust to reality." We can only really endure life if we cherish healthy illusions, if we have faith no matter how fantastic, or the kind of healthy-mindedness that shakes off, as a dog shakes off water, the disagreeables of now and the future.

DIABETES WEEK

THE American Diabetes Association has announced the fifth annual Diabetes Week, November 16 to 22, 1952. The twofold objective is to promote the discovery of diabetes in the earliest possible stage, and to stimulate interest in better treatment of the known cases of diabetes. Each year since 1948, the American Diabetes Association has engaged in a campaign of detection and education in co-operation with its local affiliated associations and with the state, county and district medical societies. During Diabetes Week, an intensive effort is made to bring the problem of diabetes to the attention of the public and the medical profession. At this time, renewed emphasis is placed on a continuing program carried on throughout the year.

The diabetes-detection campaign differs from most public-health activities in two respects. In the first place, the leadership and most of the effort are contributed by members of the medical profession. The endorsement of the American Medical Association was obtained at the outset, and the work has been carried on with the guidance and approval of organized medicine at every level. Secondly, there is no public appeal for funds. With so many appeals for money to support organizations concerned with sufferers from single types of disease, it is refreshing to learn of a medical program presented to the public without a call for contributions. The campaign is conducted solely as a program of general education and individual service to diabetic patients.

The results of past campaigns cannot easily be evaluated, but it is certain that there has been substantial benefit. Many new cases of diabetes have been discovered; it has thus been possible to protect the affected persons from needless impairment of health and even loss of life. Interest in the problems of diabetes on the part of patients and on the part of the public has been renewed, and should eventually prove to be of inestimable value in individual and community health protection.

The New England Diabetes Association has made its special effort through the "Diabetes Fair," which will be presented for the third time on November 14 and 15. At this fair, held in the Horticultural Hall in Boston from 11:00 a.m. to 10:00 p.m. on these two days, free tests for diabetes are offered to all comers. Exhibits are presented to illustrate diet and other matters. Motion pictures and film strips are shown almost continuously, being supplemented by talks and question periods. The climax of this year's program will be a public meeting held in the auditorium of the Horticultural Hall on the evening of November 14.

Members of the medical profession are urged to participate in the campaign. One method open to all physicians is to co-operate in the offer, approved by many medical societies, to perform urine tests free of charge during Diabetes Week. The time and effort required for this service can pay large dividends in terms of service to the community. Opportunities for participation in other ways are available through the various local committees on diabetes.

Diabetes presents an unusual challenge. Efforts directed toward both prevention and therapy offer rewards greater than can be found in dealing with most chronic diseases. With general recognition of this fact, the success of Diabetes Week is assured.

TOO MANY AND TOO EARLY

It is apparent that the only way in which nature achieves anything approximating a balance is by a series of ups and downs, like a see-saw, or backs and forths, like a pendulum or any other of a number of oscillatory mechanisms. Anything resembling equilibrium is a long-term proposition, consisting of a number of too littles and too lates, offset by a similar number of too muches and too soons.

There are years in which rabbits, caribou and gypsy moths multiply beyond the capacity of their food supply to sustain them, and famine and disease restore the balance; apples may be so plentiful in one year as to glut the market, or so scarce in another that ordinary people, after taxes, cannot afford to buy them. The story of the seven lean cows that devoured the fat ones in Pharaoh's dream is still remembered by countless persons who hold such references in awe — a reminder that the flood waters of the Missouri strike consternation to the farmers of its plains, whereas the Egyptians could not exist without the annual overflowing of the Nile.

This refusal of the laws of supply and demand to gel into any constant pattern is manifested in other ways. Even the number of medical students required to carry on the functions of the healing art seems never quite adapted to the needs of the generation into which they are born. Elsewhere in this issue of the *Journal* a brief comment may be found on the superabundance of medical students a century ago, in the face of which medicopedagogic profligacy the spector of an underdoctored economy is presently raised to haunt the clumsy planners of today.

It can be forecast with considerable assurance that any apparent balance will be relative and temporary, like the mush and the milk that never come out even.

Dr. Brown Sequard, of Paris, is winning golden opinions from the profession of New York. . . . He is au fait *in all that appertains to modern physiology, and his numerous* vivisections *are conducted with a delicacy and* sang froid, *which divests them of any semblance of repulsiveness.*

Boston M. & S. J., *November 3, 1852*

MASSACHUSETTS MEDICAL SOCIETY

HEARING ON ANNUAL REGISTRATION AND FEE SPLITTING

Fellows of the Society wishing to express their views on the problems of annual registration of physicians and state legislation against fee splitting are urged to attend the meeting of the Committee on State Legislation to be held at the Harvard Club, Boston, on Wednesday, November 12. Annual registration of physicians will be discussed at 3:30 p.m., and fee-splitting legislation will be discussed at 4:30 p.m. Members of the Committee on Ethics and Discipline will be present at the latter session.

BOSTON MEDICAL LIBRARY

Tomas Romay

The centenary of the death of Tomas Romay, eminent Cuban physician, was celebrated in 1949, being commemorated in 1950 by an official publication *Apuntes biograficos y discursos. Ricopilacion y prologo de Jose Lopez Sánchez*, issued by the Ministerio de Education, Direccion de Cultura, at Havana. Dr. Romay was distinguished in many fields: medicine, public health, science, sociology and politics. He was long interested in the Sociedad Economica de la Habana and was active in its affairs from 1793 until his death in 1849. He was made an honorary member of the Society in 1844 in appreciation of his services. At one time he held the high political office of secretary of the Junta de Población Blanca. He became interested in the epidemic diseases that ravaged the tropical countries, especially yellow fever and smallpox. He performed autopsies on victims of these diseases in a search for means for their prevention and control. In 1802, three years after the discovery of vaccination by Jenner, he advocated the use of vaccine for smallpox. He was a many-sided man, interested in botany, mineral waters and everything medical. Sánchez presents a chronology of his activities from 1793 to 1844, comprising 137 pages. Also reproduced are his two monographs on yellow fever,

Disertacion sobre la fiebre maligna llameda vulgarmenta vomito negro enfermedad epidemica en las Indias occidentales (Havana, 1797), and vaccination, *Memoria sobre la introduccion y progreso de la vacuna en la Isla de Cuba* (Havana, 1805). To show his versatility his elegy on the first president of the Sociedad Económica, *Elegio del excell. Señor don Luis de la Cases y Arragori . . .* (Havana, about 1800), and his paper on Bonaparte, Goday and the Spanish Monarchy, *Conjuracion de Bonaparte y don Manuel Godoy contra la monarquia Espanola*, are republished. A short biography of Romay, written in 1862 by Anselmo Suárez Romero, and previously unpublished, begins the small book, which concludes with the elegy by Manuel Costales, *Elogio del Dr. D. Tomas Romay medico honorario de la Real Camara* (Havana, 1850).

Also, Jose L. Sánchez has written an excellent and well documented biography of Romay as citizen and physician. Chapters are devoted to yellow fever, vaccination, public health, the cholera epidemic of 1833 in Havana, medicophilosophical ideas and Romay's contributions to the progress of medicine and culture. A number of chapters concern his political and social activities, and his interest in education. He wrote a large number of poems, all published under various pseudonyms and listed in appendix B. Appendixes D, E, G and I, deal with yellow fever, vaccination, cholera morbus and anatomy. Romay became interested in vaccination as early as 1803. He was influenced by the work of Hernandez,[2] published in 1801. Jenner published his original work in 1798. The Spanish work is not a translation of Jenner, according to LeFanu.[3] Sánchez's concluding chapter presents an extensive bibliography, including a chronologic list of the writings of Romay.

References

1. Sánchez, J. L. *Vida y obra del sabio médico habanero. Dr. Tomas Romay Chacón.* 420 pp. Havana: Editorial Libreria Selecta, 1950.
2. Hernández, P. *Origen y descibrumiento de la vaccina.* Madrid, 1801.
3. LeFanu, W. R. *A bio-bibliography of Edward Jenner, 1749-1823.* 176 pp. London: Harvey and Blythe, Ltd., 1951.

NEW HAMPSHIRE MEDICAL SOCIETY

FRISBIE MEMORIAL HOSPITAL DINNER MEETING

The medical staff and the trustees of the Frisbie Memorial Hospital, Rochester, New Hampshire, were recently joint sponsors of a dinner and a staff meeting with Dr. Frederick T. Hill, medical director of the Thayer Hospital, Waterville, Maine, as guest. Dr. Hill spoke on his favorite interest and hobby "The Medical Audit." A nationally known authority and promoter of first-rate professional standards in the smaller hospital, Dr. Hill was received with considerable enthusiasm and interest not only by his hosts at the Frisbie Hospital but also by representative invited guests, including staff members and trustees of the following neighboring hospitals: Wentworth Hospital, Dover, New Hampshire; Exeter Hospital, Exeter, New Hampshire; Huggins Hospital, Wolfeboro, New Hampshire; and Goodale Hospital, Sanford, Maine.

CORRESPONDENCE

ARTHRALGIA IN RUBELLA

To the Editor: I have just finished reading, in the September 18 issue of the *Journal*, the article on rubella by Lt. Robert B. Kalmansohn.

I read this with much interest since there has been a large epidemic of rubella here in York County, Pennsylvania. We understand that Lt. Kalmansohn did not intend to make this a comprehensive review although he covered the subject very well.

He does not mention a symptom, however, that was exceedingly prevalent in our epidemic, in which I saw well over 100 cases: a severe arthralgia in the hands, particularly the finger joints. This was noted in almost all my patients over ten years of age. In fact it was almost as common as the posterior cervical and postauricular lymph adenopathy. In some cases it was severe enough to limit the use of the hands for about twenty-four hours. I had a wife and two "teen" age sons with it in my own home and had an opportunity to watch this painful symptom at first hand.

It put in its appearance just as the rash was disappearing and continued for a day or so after the rash was gone.

On reviewing the section on rubella in Holt and McIntosh's *Diseases of Infancy and Childhood* I find no reference to this symptom.

In fifteen years of a large, general practice I have seen only several cases of rubella; this was the first large epidemic.

Was this late symptom of arthralgia in the hands peculiar to our epidemic or is it a symptom that has been neglected in the past because of its late appearance and the fact that scant attention has been paid to rubella?

In cases in which one is in doubt whether the disease is measles, rubella or scarlet fever this tardy symptom of arthralgia might establish the diagnosis.

In this community we have also had at least 5 girls pregnant, with rubella occurring during the first trimester of pregnancy.

I have been a subscriber to the *Journal* for less than a year but in that time have found it more stimulating and readable than anything that comes to my desk. The recent symposiums on the thyroid and on diabetes mellitus have been excellent.

PHILIP A. HOOVER, M.D.

Dallastown, Pennsylvania

BOOKS REVIEWS

The Story of the Rockefeller Foundation. By Raymond B. Fosdick. 8°, cloth, 336 pp. New York: Harper and Brothers, 1952. $4.50.

The Rockefeller Foundation was instituted in 1913 by John D. Rockefeller, Sr., with a grant of over $182,000,000. Mr. Fosdick was president of the Foundation for twelve years, 1936–1948, and was closely identified with the other Rockefeller benefactions; he is therefore well fitted to write this history. In an introduction the various Rockefeller funds are identified, and their particular fields outlined. The Foundation at first was interested in the advancement of medical research and education, including the control of the hookworm and of yellow fever, and in the field of public health. Later, the fields of experimental biology, agriculture, the social sciences and the humanities became major endeavors. The work for libraries has been notable. The story is written primarily for laymen and in a simple, understandable manner. The publishing is excellent in every way, and the book is recommended for all libraries, general and medical.

JAMES F. BALLARD

Jewish Medicine. By Solomon R. Kagan, M.D. 8°, cloth, 575 pp., with illustrations. Boston: Medico-Historical Press, 1952. $10.00.

This latest book of Dr. Kagan is published in commemoration of his sixtieth birthday, sponsored by a committee of distinguished physicians, scientists and scholars. Preceding the text proper is a short biography of the author and tributes from Max Neuburger, Ruben Friedman, Hyman Morrison and Abraham Levinson. Dr. Kagan originally prepared for the rabbinate but decided to study medicine and received the degree of doctor in medicine from the University of Dorpat in 1917. He came to the United States in 1922 and practiced his profession until 1935, when he was forced to retire because of illness. The first chapter discusses ancient Jewish medicine based on the Bible and the Talmud. The remainder of the book is essentially a biographic dictionary arranged by periods: Medieval Jewish medicine, the Renaissance, the seventeenth and eighteenth centuries and modern Jewish medicine. The material in this last division is arranged by subjects and chronologically within the subjects. There is an index of names. The book contains a wealth of information about physicians and should be in all historical collections, medical and general.

JAMES F. BALLARD

The Cost of Health. By Ffrangcon Roberts, M.D. 8°, cloth, 200 pp. London: Turn-Stile Press, 1952. 16s.

Dr. Roberts discusses frankly the National Health Service of Great Britain. The Beveridge *Report on Social Insurance and Allied Services* of 1942 estimated the cost of a comprehensive health service at £170,000,000, and that by 1965 the natural adjustments would maintain that figure. In 1952 the cost has reached £400,000,000 and would be much higher except that the Treasury has imposed a ceiling at this point. The author points out that the cost can soon reach an amount that the nation cannot afford unless some curtailment is made in the services. He discusses the evolution and expansion of medicine and the nature of medical progress, as well as the relations of national health and wealth, the mutual obligations of the individual and the state, private and social insurance and the economic value of the physician. This important book is recommended for all libraries, public and medical.

JAMES F. BALLARD

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Clark's Applied Pharmacology. Revised by Andrew Wilson, M.D., Ph.D., F.R.F.P.S., reader in applied pharmacology in the University of London at University College, London, and University College Hospital Medical School; and H. O. Schild, M.D., Ph.D., D. Sc., reader in pharmacology in the University of London at University College, London. Eighth edition. 8°, cloth, 691 pp., with 120 illustrations and 47 tables. Philadelphia: Blakiston Company, 1952. $7.00.

This standard British book, first published in 1923, has gone through ten previous reprintings, and has been translated into Spanish and Chinese. Dr. A. J. Clark, the original author, died in 1941, after completing the seventh edition. The text of this new edition has been completely revised and material added, including sixty new illustrations, principally on the action of drugs on man. There is a good index. The printing was done in Great Britain.

Memòrias do Instituto Oswaldo, Cruz, Rio de Janeiro, Brasil. Marco de 1951. Tomo 49. 4°, paper, 683 pp., with illustrations. Rio de Janeiro: Serviço Gráfico do Instituto Brasileiro de Georgrafia e Estatistica, 1951.

This volume of an important series contains a long monograph on trematodes: *Revisao da familia* Eucotylidae, Skrjabin 1924 (*Trematoda*). The sixteen shorter articles deal with tropical insects, parasites and diseases, including one on experimental leprosy.

The Internship. By Roscoe L. Pullen, M.D., professor of graduate medicine, director of the Division of Graduate Medicine, and vice-dean, Tulane University of Louisiana School of Medicine, senior visiting physician, Charity Hospital of Louisiana at New Orleans, consultant in medicine, Veterans Administration Hospital, New Orleans, and consultant to the Surgeon General, Department of the Army, Washington, D. C. 8°, paper, 35 pp. Springfield, Illinois: Charles C Thomas, 1952. $1.25. (Publication No. 154, *American Lecture Series.*)

The author discusses in this small pamphlet the factors influencing internship, educational adaptation of present internships and suggested modification of the internship. Dr. Pullen's proposal is to place the fourth-year medical students on a twelve-month basis, with a one-month vacation staggered throughout the year. The students during this year would be rotated through the major clinical fields of internal medicine, surgery, obstetrics and gynecology and pediatrics. In the fifth year, the graduate would enter the internship proper, which would be a continuation of the fourth year.

NOTICES

BOSTON GASTROENTEROLOGICAL SOCIETY

A meeting of the Boston Gastroenterological Society will be held in the new Cheever Amphitheater of the Boston City Hospital on Thursday, November 6, at 8 p.m.

There will be a symposium on "Jaundice" with a panel discussion by Drs. Chester M. Jones, Francis D. Moore, Franz J. Ingelfinger and I. R. Jankelson.

All physicians are cordially invited.

LECTURES ON CANCER RESEARCH

The following lectures, sponsored by the Children's Cancer Research Foundation and the Department of Pathology, Harvard Medical School, will be presented at The Children's Hospital on the dates indicated:

November 12, at 12 noon. Dr. Max Wintrobe, head of the Department of Medicine, University of Utah School of Medicine, will speak on the subject "Studies on the Functions and Metabolism of Copper" in the auditorium of the Jimmy Fund Building, 35 Binney Street, Boston, December 2, at 5 p.m. Dr. Carl V. Moore, professor of medicine, Washington University School of Medicine, St. Louis, will speak on the subject "Therapeutic Approach to the Anemia of Chronic Bone Marrow Failure" in the Fourth Floor Conference Room of the Jimmy Fund Building, 35 Binney Street, Boston.

NEW ENGLAND CONFERENCES ON ALLERGY AND RELATED SUBJECTS

The fifth meeting of the New England Conferences on Allergy and Related Subjects will be held on Wednesday afternoon and evening, November 19. The afternoon program will consist of the presentation of cases. This part of the program, conducted by Dr. Walter S. Burrage, will be held from 3:30 to 5:30 o'clock in the Bigelow Auditorium, White Building 3A, Massachusetts General Hospital, Fruit Street, Boston.

The evening program will take place at the Sheraton (Copley) Plaza Hotel, Copley Square, Boston, Massachusetts, at 8:30 o'clock. Drs. Louis Tuft, Lewis W. Hill and Albert H. Coons will participate in a panel discussion on allergens and antibodies with Dr. Francis C. Lowell as moderator.

Arrangements have been made for a dinner at 7 p.m. at the Sheraton Plaza Hotel for the convenience of those attending the program. Reservations may be made before November 15 with Dr. Irving W. Schiller, 65 East Newton Street, Boston 18; a check for $5.50 to cover the expenses of the dinner should be enclosed.

All members of the medical profession are cordially invited.

POSTGRADUATE COURSE IN GENERAL MEDICINE

The Middlesex West District Medical Society and the Postgraduate Medical Institute are sponsoring a course of twelve sessions as part of their postgraduate educational program for the physicians of this area. These are to be con-

ducted mainly in the interests of the general practitioner. They are to be held on alternate Monday evenings from 8 to 10 o'clock, beginning October 20, 1952, in the Conference Room at the Cushing Veterans Administration Hospital, Framingham, Massachusetts.

The program is as follows:

November 3. The Medical and Surgical Approach in the Treatment of Hypertension. Drs. Morton Brown and George Whitelaw.

November 17. The Use and Abuse of Antibiotics. Dr. Louis Weinstein and others.

December 1. Electrolytes and Water Balance. Dr. Jack D. Rosenbaum.

December 15. Cortisone and ACTH: Their application in the treatment of disease. Dr. Maurice B. Strauss and others.

December 29. Hematuria. Drs. William Holtham and Herbert S. Talbot.

January 12. Anticoagulants in the Treatment of Disease — Theory and Practical Use. Dr. Robert Goldstein.

January 26. Anemias. Dr. William Dameshek and others.

February 9. Practical Clinical Application of Radioactive Isotopes. Dr. Joseph Ross and others.

February 23. Menstrual Disorders. Dr. Somers H. Sturgis.

March 9. Care of Newborn. Dr. David Gitlin.

March 23. Dystocia. Dr. Daniel J. McSweeney.

Attendance at the course will be open to all physicians, regardless of whether or not they are members of the Society. There will be a registration fee of $5.

NEW ENGLAND CARDIOVASCULAR SOCIETY

A meeting of the New England Cardiovascular Society will be presented by the Boston City Hospital and the Massachusetts General Hospital on Monday, November 17, at 8:00 p.m., at the Dorothy Quincy Suite of the John Hancock Hall, 180 Berkeley Street, Boston.

PROGRAM

Boston City Hospital. Laurence B. Ellis, M.D. presiding:

The Use of the Anticoagulant Phenylindanedione in Ambulatory Patients.
Drs. Frank Drinan, H.S. Sise and W. C. Maloney.

Rheumatic Activity in Patients with Mitral Stenosis Undergoing Valvuloplasty.
Pathological Aspects. Drs. J. P. Decker, C. Van Z. Hawn, and S. L. Robbins.
Clinical Aspects. Dr. W. F. McNeely.

The Diagnosis of Mitral Regurgitation. Dr. W. H. Abelmann.

Massachusetts General Hospital. Edward F. Bland, M.D. presiding:

Misleading Auscultatory Signs in Mitral Stenosis. Drs. Allan L. Friedlich, Gordon S. Myers, Edward F. Bland and Howard B. Sprague.

The Relation of the Electrocardiogram to Red-Cell Chemical Changes in Diabetic Acidosis. Drs. Ernest Craige and Hans Keitel.

Studies of the Regulation of Cholesterol Synthesis in the Rat. Drs. Ivan D. Frantz, Jr., and Donald S. Fredrickson.

Interested physicians, medical students and members of the New England Postgraduate Assembly are cordially invited to attend.

Free parking facilities are available on St. James Street above Clarendon Street. (No attendant on duty.)

ALPHA OMEGA ALPHA LECTURE

The Boston University Chapter of Alpha Omega Alpha will sponsor its first lecture of the current year on Thursday, November 13 at 5:00 p.m., in the Boston University School of Medicine Auditorium, 80 East Concord Street. Dr. E. Cowles Andrus, associate professor of medicine, Johns Hopkins University School of Medicine, and physician, Johns Hopkins Hospital, will speak on the subject "The Surgery of Mitral Stenosis and Its Physiologic Consequences."

This address is open to the medical profession. A hearty welcome is extended to all.

LAHEY CLINIC LECTURES

Lectures will be held on the following dates in the Joslin Auditorium, Lahey Clinic, at 7:30 p.m.:

NOVEMBER 12

Medical motion picture entitled "Gastric Resection" (this is a special innovation in three-dimensional photography made by Dr. Samuel F. Marshall and the Worcester Film Company).
Radial Surgery in Treating Cancer. Dr. Samuel F. Marshall.
Preoperative and Postoperative Dietary Management. Dr. Francis E. McDonough.

NOVEMBER 19

Irritable Bowel. Dr. Sara M. Jordan.
Anorectal Disease. Dr. Neil W. Swinton.

NOVEMBER 26

Diseases of the Intestines. Drs. Richard B. Cattell and Everett O. Kiefer.

DECEMBER 3

Diseases of the Breast. Dr. Cornelius E. Sedgwick.
Fluid and Electrolyte Balance. Dr. George O. Bell.

DECEMBER 10

Hoarseness. Dr. Kenneth S. Oliver.
Disease of the Esophagus. Dr. Walter B. Hoover.

DECEMBER 17

Endoscopy. Dr. Kenneth S. Oliver.
Vertigo and Deafness. Dr. Frank D. Lathrop.

Visitors are welcome.

VETERANS ADMINISTRATION COURSE IN PSYCHIATRY AND NEUROLOGY

The Veterans Administration is instituting a four-month intensive training course in psychiatry and neurology to fit the needs of physicians without such previous training who are assigned to duty in 22 predominantly psychiatric hospitals. Physicians who have been engaged in general practice may request this training upon applying for a position at one of these hospitals.

The course will be held at Veterans Administration hospitals in Coatesville, Pennsylvania, and Palo Alto, California, and there will be a joint Downey–Hines, Illinois, program near Chicago, Illinois. Physicians will be employed at salaries commensurate with their training and experience (ranging from $5,500 to $11,800 per annum) and assigned to the course with travel and per diem for the four-month period.

Information and applications may be obtained from local Veterans Administration hospital or regional office, or from the Chief Medical Director, Veterans Administration Central Office, Washington 25, D. C.

FIFTH ANNUAL HARVARD LECTURE

The fifth annual Harvard Lecture will be given by Dr. Edward D. Churchill, John Homans Professor of Surgery, Harvard Medical School, and chief of the Surgical Services, Massachusetts General Hospital, at the University of Colorado Medical Center on Friday, November 7, at 5:00 p.m. The lecture is entitled "The Segmental Structure of the Lungs."

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 6–DECEMBER 8 AND MARCH 2–MAY 4. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 540, issue of October 2.

OCTOBER 7–DECEMBER 9. Massachusetts Department of Mental Health. Course in Child Psychiatry (Pediatric Neuropsychiatry). Page 540, issue of October 2.

NOVEMBER 1–29. Springfield Hospital Educational Program. Page 623, issue of October 16.

NOVEMBER 2–7 and 10–21. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

NOVEMBER 3–MARCH 23. Postgraduate Course in General Medicine. Page 697.

NOVEMBER 5. Greater Boston Medical Society. Page 661, issue of October 23.

NOVEMBER 5. Massachusetts Society of Examining Physicians. Page 661, issue of October 23.

NOVEMBER 6. New England Hospital. Page 661, issue of October 23.

NOVEMBER 6. Boston Gastroenterological Society. Page 697.

NOVEMBER 7. Fifth Annual Harvard Lecture. Notice above.

NOVEMBER 9 AND 10. American Society for the Study of Arteriosclerosis. Page 78, issue of July 10.

(Notices concluded on page xi)